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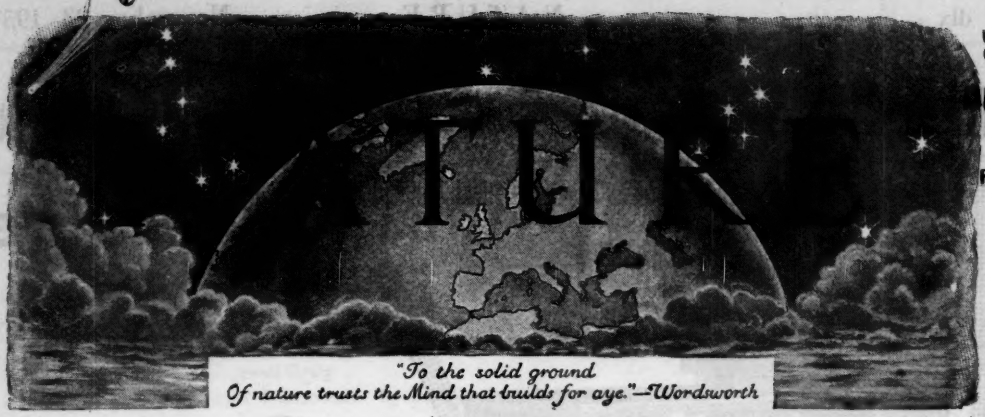

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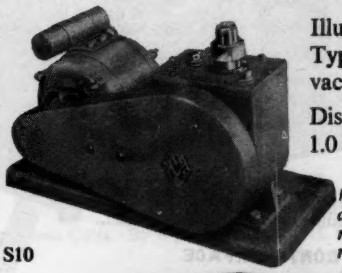

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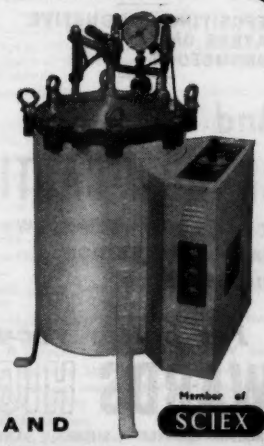

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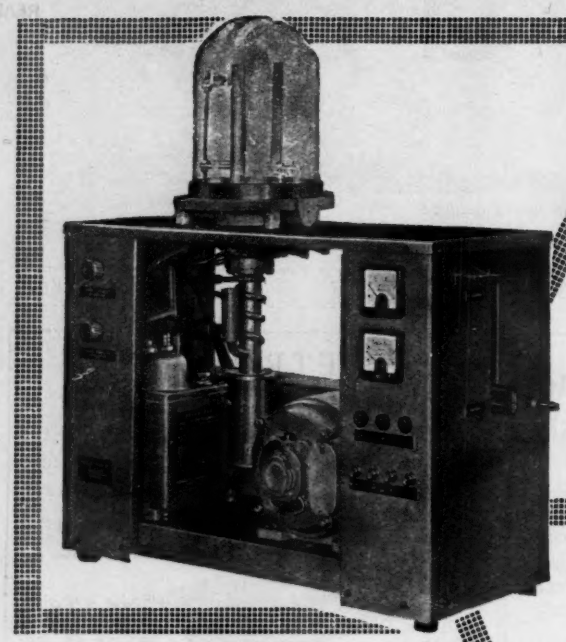

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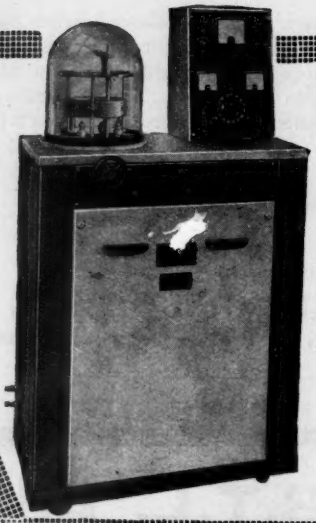

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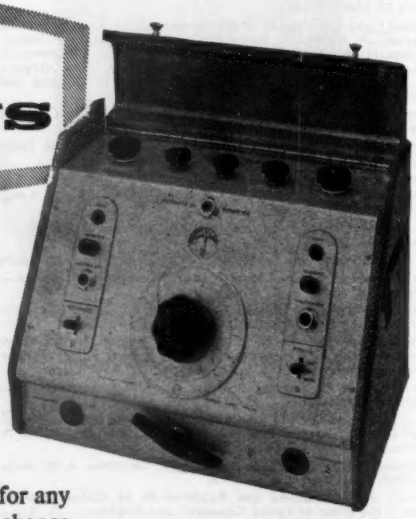

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SCIENTIFIC AND TECHNICAL MAN-POWER IN BRITAIN

THE tenth annual report of the Advisory Council on Scientific Policy, covering the period July 1, 1956, to June 30, 1957*, again deals largely with the shortage of trained man-power in Britain which remains the chief limiting factor to scientific effort. During the year, however, the Council was also concerned with the balance and scale of the national effort in research and development in relation to national needs. The structure or organization of that effort is still under consideration, and the need for much more statistical information as to its magnitude is stressed; but the present report discusses chiefly the magnitude of the nation's research and development effort and its distribution, and questions of scientific man-power and its utilization, particularly those presented by the emigration of scientists and engineers and the Government's continued disregard of the Council's recommendations about scientific libraries.

The Advisory Council recognizes that accurate information as to the distribution of the effort in research and development in Britain is extremely difficult to obtain. The dividing lines between research, development and production are often arbitrary and indistinct, and even if adequate statistics were available, they would be liable to considerable error. Any attempt to apportion expenditure—or man-power—between teaching and research, which is inevitable in assessing the country's effort in fundamental research, is again necessarily arbitrary. Nevertheless, the Advisory Council rightly holds that, despite the uncertainties in statistics, the attempt should be made. Any figures obtained would give at least some order of magnitude to a general picture and might well indicate any gross deficiency or lack of balance.

The inquiries as to expenditure by industry on research and development on which the report on "Scientific and Engineering Man-power in Great Britain" (London: H.M.S.O., 1956) was based, and other inquiries of the universities and nationalized industries, indicate that in 1955–56 about £300 million was spent on research and development in Great Britain. Of this, £185 million (a figure which may be subject to an error of £40 million) was spent by private industry (but largely paid for by the Government), £4 million by the nationalized industries, and £5 million by the research associations. Government expenditure amounted to £65·5 million on defence research and development, and in the civil sector to £12·5 million by Government departments and £10 million by the research councils, including £1 million for the Agricultural Research Council and Medical Research Council units attached to universities. University research expenditure is estimated at £14·5 million and research expenditure by other organizations at £3·5 million, of which £2 million is on defence research.

The total expenditure on research and development in Britain thus corresponded to about 1·6 per cent of the gross national product (at market prices) for the year 1955, industry's own expenditure on research and development being about 0·8 per cent of the industrial output. These figures compare with an expenditure estimated by the National Science Foundation for the United States at 1·5 per cent of the gross national product in 1953 and an industrial expenditure of about 1·9 per cent of net output. Since 1953, moreover, expenditure on research and development in the United States has risen more rapidly than the gross national product. Comparable figures are not available for Western European countries the economies of which are closer to that of Britain in pattern and scale, but the Advisory Council states that it understands that a number of such surveys are contemplated and that the United Kingdom is offering to assist through the European Productivity Agency.

Government expenditure on research and development during 1956–57 amounted to some £224 million (of which £177·5 million was on defence, or roughly 75 per cent of the total), and not counting the contribution from Government sources expended by the universities or the nationalized industries. Expenditure by the Atomic Energy Authority is included, both under defence research and under civil research and development, but without being distinguished. The estimates for defence research and development include some £16 million for expenditure on capital projects, sites, maintenance of buildings, and £7 million for work done on a repayment basis for private industry and other organizations. The estimates of university expenditure are based essentially on an analysis of published accounts for 1954–55, and in arriving at the figure of £9·8 million available to the universities for civil research from Government departments, including £7·5 million from the Treasury grant in aid of recurrent expenditure, it has been estimated that £4·3 million is spent on research in science and technology, £2·7 million on medical research and £0·5 million on agricultural and medical research. Since a further £2 million from Treasury grants for non-recurrent expenditure on capital works has been included, the total is again too high to give a true measure of recurrent expenditure; but, on the other hand, the exclusion of expenditure on research and development in overseas territories makes the figures included for Colonial research and development too low to give the full measure of the national effort in that field either under the Colonial Research Council or the Department of Scientific and Industrial Research.

* Annual Report of the Advisory Council on Scientific Policy, 1956–1957. Pp. 27. (Cmnd. 278.) (London: H.M. Stationery Office, 1957.) 1s. 4d. net.

While three-quarters of the expenditure on research and development was provided from Government sources, only about 30 per cent was actually carried out in Government or Government-controlled establishments. About 68·5 per cent of research and development was carried out by industry; but only 23 per cent was financed by industry, the rest being mainly in the form of defence contracts of various types. About 60 per cent of the total expenditure came under the heading of Government expenditure on defence research. Analysed according to the sectors in which it was carried out, Government expenditure on research and development accounted for 21·9 per cent of the total; civil research and development by the Government departments for 4·1 per cent and under the research councils for 3·3 per cent; by the nationalized industries, 1·3 per cent; by private industry, 61·7 per cent; by the research associations, 1·6 per cent; and by the universities, 4·8 per cent.

The man-power picture is similar. Of some 46,600 scientists and engineers estimated as engaged in research and development in 1955–56 in Great Britain, 4,900 were employed in the Defence departments, 1,500 on civil research in Government departments, 2,500 by the research councils, 2,500 by the Atomic Energy Authority, 1,000 in nationalized industries, 23,800 in private industry, 1,400 in the research associations, and 9,000 in the universities (assuming university teachers spend 50 per cent of their time on research), and including 5,300 graduate research students. Not far short of half were employed on defence work, either in Government establishments or in industry, although a significant proportion of the work done under defence contracts yields results of value to the development of civil industry and our export trade.

The analysis requires to be carried further and based on much fuller figures before we can say with any confidence that there is no lack of balance in our research effort and draw any sound conclusions as to its magnitude or distribution. On the figures presented here, it is no more possible than on those cited in last year's debates on the Department of Scientific and Industrial Research Bill to say that our effort in nuclear research, for example, is excessive or causing distortion. Nor, as the Advisory Council rightly observes, is it possible to lay down any proportion of the total national effort on research and development which should *a priori* be devoted to the civil sector. Determination of the actual amount which must be spent to secure that the country's defences are adequate rests on military and political considerations outside the Council's competence. Nevertheless, the figures it has collected seem to justify the considered view that the resources devoted to civil research and development have been, and still are, far too small for a country like Britain, the competitive position of which in world trade depends upon the economic development of new products and new processes, and where achievement of a rising standard of living depends mainly on success in increasing the productivity of the labour force.

The Advisory Council has for several years past been concerned with the possibility of increasing the scientific effort in the many industries where that effort is far too small, and the Department of Scientific and Industrial Research in particular is closely engaged with such problems. In the present report the Advisory Council does not discuss such problems further, but is concerned first with the transfer from defence to civil research and development which the cuts in defence should permit and with measures which might increase the effectiveness of research at the universities. It is hoped that some immediate improvement in the man-power situation will result from the absorption without delay into civil work of scientists and engineers released from defence work, and also that the major proportion of new graduates in science and engineering coming forward now and for some time to come, and suitable for research and development work, will go into civil industry. But the Council also recognizes that even with the 6 per cent increase in the output of qualified scientists and engineers in 1956 compared with 1955, and with a 20 per cent increase between 1954 and 1956 in the number of students entering the science and technology departments of universities, it must still be concerned to see that sufficient scientists become teachers to provide adequate grounding in mathematics and science for the larger number of children entering the secondary schools in 1958.

The Advisory Council was asked for advice as to the desirability of making greater use of Government defence research establishments for civil purposes. At present such work for other Government departments and private industry accounts for about 5 per cent of the work done in these establishments. The Advisory Council accepts the general position and agrees that such establishments could sometimes with advantage undertake civil work where it would otherwise be impossible to make full use of equipment, facilities or research teams. Nevertheless, the Advisory Council is undoubtedly right to urge that staff freed by the defence cuts should not in general be retained in defence establishments. It is entirely sound that civil research should be carried out so far as possible in civil establishments, and the Advisory Council is only disposed to admit the placing by firms of research contracts with defence establishments as promoting the use of more and more of our research potential in the interest of the civil sector of the economy.

The biggest and most important problem is likely to arise in industry, and the Advisory Council's fear that, in the short run, expansion in civil research and development may not be concomitant with the decrease in defence contracts is borne out by some of the disclosures in the report on industry and technical progress. The Council suggests that if the total civil research effort falls, the use of civil research and development contracts should be re-examined. Arrangements have been made as a result of recom-

mendations in the Advisory Council's 1952–53 report for the Department of Scientific and Industrial Research to act as a central focus in all matters relating to the placing of development contracts by Government departments, to keep in touch with what is being done in other departments, to collect, evaluate and disseminate information about such projects, and to provide advice and assistance when required. So far the response has been small, but the Advisory Council is confident that the scheme should be useful.

If the Advisory Council is wise to seek to shift the balance in research effort from the Government sector to that of private industry and the universities, it rather surprisingly makes no comment on the slender efforts made by the nationalized industries. Somewhat surprisingly, too, it seems content to accept the present expenditure on scientific research in British universities as a reasonable proportion of the total efforts on research and development effort—5 per cent in 1955–56. Its figure of £14·5 million is reached after taking into account all data available through published university accounts, the research councils and the University Grants Committee, and it includes about £2 million from research contracts placed by Government with industry. The Advisory Council does not consider that this 16 per cent (compared with the 50 per cent out of 285 million dollars in American universities in 1953–54) represents any cause for alarm, although any marked increase in sponsored research would be most undesirable. Again, it disregards entirely the contribution from the colleges of technology, on which the Willis Jackson Committee rightly laid some stress, though it is here that the question of sponsored research might prove more difficult.

Some contract work is almost inevitable, and the Advisory Council goes to the root of the matter in pointing out that Government support of free scientific research in universities, through the Treasury grant, the research councils and the Royal Society, should always be at a level which permits university research to flourish without increasing resort to contract work—an observation which is equally valid in respect of research in the colleges of technology. In general, however, it accepts the proportion of the nation's scientific man-power engaged on research in the universities as reasonable, and while this view may well be open to challenge, the challenge will be the stronger if made when discussing the balance of research effort in the main fields of work, or possibly in reviewing the arrangements for co-ordination of effort into which the Advisory Council is still inquiring. In this connexion, indeed, it is pointed out that the universities will be severely taxed during the next ten years to find the staff and accommodation for the increasing load of undergraduate teaching; but that additional teaching staff in itself means additional university research, and the increased number of undergraduates should also lead to an increase in the number of postgraduate research assistants.

Meanwhile, however, the Advisory Council makes one comment of first-class importance in reference to the effectiveness of university research to which Sir George Thomson also referred trenchantly in his recent Fawley Foundation Lecture. It believes that the proportion of supporting staff to professional workers is too low, and that a substantial increase in the number of technicians employed would do much to increase the value and productivity of the research effort of the universities. Indeed, it is probable that there are few ways in which a comparatively small expenditure could do more to eliminate the waste of highly skilled man-power, and the Advisory Council might have done well to frame its conclusion in the form of a recommendation to the Lord President of the Council, or perhaps to the University Grants Committee. Left in its present form, it is unlikely to receive effective backing.

In commenting on the transfer of highly specialized man-power from defence to civil work, the Advisory Council refers to the grave danger that, unless efforts are made to assist highly qualified men to find new jobs which they will regard as satisfactory, emigration may increase, particularly to the United States and Canada, where there is a large unsatisfied demand for such men. During the year, the Council made inquiries from the universities, the Board of Trade, professional institutions and the immigration authorities in the United States and Canada as to the immigration of highly qualified scientists and engineers, and the subject is discussed in a separate section of the report. The indications are that, over the past seven years, 1950–56, about 190 postgraduate chemists and 145 postgraduate physicists left the universities to take employment or fellowships in the United States or Canada. These figures represent about 6 per cent and 10 per cent, respectively, of the average annual numbers of postgraduate chemists and physicists who left the universities during the last five of these years, and the number was greater in 1956 than in any previous year. In the same period, some 410 chemists and 130 physicists accepted postgraduate fellowships in the United States or Canada, about 40 per cent remaining there on completion of their fellowships; if the information obtained from four of the largest professional institutions is typical, about 8 per cent of the increase in membership in 1956 left the country that year. Figures of immigration into Canada and the United States indicate that the number of emigrants from the British Isles who described themselves as engineers took an upward turn in 1956 after falling between 1953 and 1955; and if inquiries about posts abroad indicate a serious intention to emigrate, there may be a big increase in the number of engineers who emigrate in 1957.

The evidence is not entirely consistent—a Gallup poll at Cambridge seemed to indicate that no more than 1 per cent were serious prospective emigrants, although three times as many would be considering emigration; the Advisory Council recognizes that its conclusions need checking by statistics collected

on a more systematic basis and it has asked the Committee on Scientific Man-power to keep the situation under review. It also recognizes that to a certain extent emigration is beneficial to British interests, and if there were no current shortage, an increase in the movement would be welcomed, both in view of the growing need of the less-developed countries for technical assistance and because of the benefits to be reaped in return. As it is, the problem is to strike a balance, and the Advisory Council suggests further that factors which encourage young scientists and engineers holding fellowships or studentships in the United States or Canada not to return to Britain should, if possible, be removed; for example, if industry would arrange to set up an organization in the United States and Canada to interview graduates on behalf of United Kingdom employers the return flow might be increased. Again, it suggests that more British scientists and technologists should be encouraged to do postgraduate work in Europe, and that more publicity should be given to the fact that Department of Scientific and Industrial Research and some other fellowships can be held in Europe.

Higher salaries and better equipment and facilities for research in American universities are mentioned as the main inducements which attract young research students from United Kingdom universities; but otherwise the Advisory Council does not touch on the fiscal considerations stressed by the Chancellor of the Exchequer in his last Budget speech. If further inquiry should establish a continuing and substantial increase in the emigration of such highly trained professional men, the Advisory Council may well have to urge such considerations, among others, very strongly on the Government. It cannot leave the problem alone until, as with the failure to implement the Council's recommendations about scientific libraries, Britain's scientific and technological capacity is endangered.

In this matter of scientific libraries, the Council is again only able to report trifling progress. Although a unit has been set up by the Department of Scientific and Industrial Research to implement the planning of a National Scientific Lending Library, search is still being made for a suitable location outside London for a National Lending Library of Science and Technology. Agreement has been reached, in principle, for the transfer in due course of part of the collection of the Science Museum Library to the new National Library, but it appears that acquisition of a suitable site for erection of the National Reference Library of Science and Invention, in conjunction with a new Patent Office Library, is still under consideration. The Advisory Council repeats its warning that the needs which these libraries are intended to meet are continually growing, and that the longer action is deferred, the more difficult it will become to find adequate solutions to these problems of the dissemination and utilization of scientific information.

It is a pity that the bearing of these projects, and indeed of the conception of the Science Centre itself, both on the efficient utilization of scientific man-power and on the application of the results of research, has not been presented in such a way as to bring out the wastefulness and costliness of the Government's dilatoriness and inaction. The history of the whole project, its implications and possibilities, should make it plain where the responsibility lies and frustrate any attempt to make party political capital out of a dereliction of duty in which both political parties share. The over-riding lesson to be learned from the Advisory Council's latest report is in fact just this danger of allowing preconceived ideas or political doctrine to prevent the action to which impartial inquiry points. The wise use of the limited resources of Britain in research and development demands, indeed, accurate knowledge and sound judgment: it demands equally vision and determination, impartiality and courage.

MANAGEMENT IN INDUSTRY

Effective Industrial Management

By James L. Lundy. Pp. xviii+588. (New York and London: The Macmillan Company, 1957.) 44*s*.

THIS is a remarkable book. Remarkable because, symbolically, it clearly shows why industry in the United States is so much more productive than in Britain; and because it deals with all aspects of management and nearly all in a highly competent matter. It is equally noteworthy because, unwittingly, the author has revealed the inadequacies of certain British publications which masquerade as authoritative works on some aspects of management studies.

The fundamental reason for the difference in productivity between American and British industry is brought out in the introduction to this book. In many colleges and universities in the United States the industrial engineering and management curricula include an introductory survey on management as a prerequisite for more specialized courses. This book has been prepared as a text for these introductory courses. Yet apart from the usual background material illustrating the development of modern methods of management, the book contains chapters on topics which even now are practised in comparatively few firms in Great Britain and which even so-called progressive firms are chary of introducing. These include certain accounting and budgetary controls, inspection and quality control, the latter including the use of statistics, various job evaluations, merit-rating and incentive schemes, operational research, inventory control and the means of evaluating purchasing performance. Their mere inclusion in an elementary text-book for introductory courses in management shows how much more objective is the American approach.

The second feature which makes this book so remarkable is its comprehensive nature. Sections are introduced dealing with all aspects of management including finance, sales, organization, research and development, production and maintenance, work study, materials handling, design, purchasing, production control, inspection, quality control, transport and all aspects of the personnel function.

With its American connotations the chapters dealing with the personnel function of management is of least relevance to British industry; the rest of the book could be used by any manager in a British firm wishing to improve his knowledge of particular functions or to strengthen his grasp of management as a whole. Lundy deserves high praise for the lucid way in which he has presented so many topics so authoritatively in such a short space.

Of the third reason which makes this book so remarkable little need be said. Until management is taken seriously as a subject worthy of study in graduate and postgraduate courses at universities, British text-books will continue to be written by men who are academically and intellectually inadequate. We have no comparable book to this in Britain; the need grows greater daily. T. H. HAWKINS

EVERYMAN'S PARASITOLOGY

Animals Parasitic in Man

By Dr. Geoffrey Lapage. (Pelican Book No. A394.) Pp. 320+8 plates. (Harmondsworth, Mddx.: Penguin Books, Ltd., 1957.) 5*s*.

THERE is a deplorable lack of knowledge and much prejudice among the general public about the parasites afflicting mankind, and even the medical man, who is expected to treat the diseases caused by them, is not much better off, owing to the neglect of parasitology in the medical curriculum. The publishers and editors of the Pelican Medical Series have therefore performed a valuable service in producing a book on this subject written by a well-known parasitologist of wide experience and erudition. As stated in the foreword and preface, this book is intended for a wide range of readers, including not only educated laymen but also junior and senior members of the medical profession, as well as biologists in general.

Instead of a conventional systematic account of the animal parasites, the author has dealt with the subject in a comparative way, from the point of view of the gradual complication of their life-cycles and the patterns of host–parasite relations. This method of approach provides the reader with an evolutionary background to the natural history of parasitic infections.

In an introductory chapter the author defines the concept of parasitism in its various manifestations. In the next chapter a brief account is given of the main zoological subdivisions to which the animal parasites belong, followed by a discussion of different types of life-histories, hosts and modes of transmission of the infections. The following five chapters are devoted to parasites with monogenetic, digenetic and polygenetic life-cycles, comprising helminths and protozoa, the bionomics, structure and host–parasite relations of which are described in some detail. Separate chapters are allocated to malaria parasites and trypanosomes and the diseases caused by them, while in another an account is given of animals parasitic in or on the skin (fleas, lice, fly maggots and mites) and of blood-suckers, such as biting insects and ticks, as well as leeches and bats. In each case, essential anatomical structures of the parasite, its course of development and method of transmission, as well as its effect upon the host, are adequately described. Important features of this book are the illustrations and diagrams, which—with the appropriate captions—give a clear picture of the life-histories and bionomics of the parasites described in the text.

In the last two chapters Dr. Lapage considers the effect of a parasitic life upon the pathogens and the reactions of the host to infection (resistance and immunity), and winds up with a short discourse on the methods of control of infections.

The author has succeeded admirably in the task of providing an instructive and stimulating book suitable for every type of reader: to the non-scientist it opens a new and fascinating field of knowledge, while the medical man and biologist are introduced to the essentials of parasitology, and even the professional parasitologist will find it useful as a 'refresher'. Unlike some other writers of popular science books, Dr. Lapage has avoided vulgarization, for, although written in simple non-technical language, which can be understood by the non-initiated reader, the biologist can rest assured that the recognized scientific terminology and the exact zoological nomenclature are adhered to throughout the text.

Those readers whose interest has been sufficiently aroused will find at the end of the book a useful list of references for further reading. There is also a detailed subject-index of about fourteen pages.

It is to be hoped that this book will meet with the success it deserves. Last—but not least—to have produced a book of such high quality at such a low price is an achievement of which the publishers can be justly proud. C. A. HOARE

HISTO-PATHOLOGY

Histological Technique for Normal and Pathological Tissues and the Identification of Parasites

By H. M. Carleton, with the collaboration of R. A. B. Drury. Third edition. (Oxford Medical Publications.) Pp. xvi+343. (London: Oxford University Press, 1957.) 30*s*. net.

THIS is the third edition of the late H. M. Carleton's useful book on histological technique. It contains not only straight histological technique, but also many current pathological and parasitological methods. All the methods in the book have been carefully tried by either Carleton or R. A. B. Drury; the latter collaborated especially in histo-pathological and bacteriological methods, and techniques for spirochætes. This edition contains fifty-five fewer pages than the first (1926), and yet covers the modern ground very well indeed. Carleton and Drury's book is the only work of this kind in the English language, because of the special parts of the biological field it covers. It is excellent for the zoologist, cytologist and parasitologist to have at his disposal a small volume of this kind, and there is no doubt that it will stimulate the younger workers to try techniques outside their fields. From this point of view—and it is what Carleton intended—the book should be most helpful in the coming years. For the small laboratory, for science laboratories in schools, and for people who have to work in laboratories abroad, this book is warmly recommended.

How far such books will survive in the future, with the impact of electron microscope technique, is

a moot point. One supposes, however, that medical and junior biology students will always have to study, with the optical microscope, sections prettily stained by current histological methods.

The frontispiece has a photograph of Harry Carleton. No doubt we all become less beautiful with age, but to those who have other photographs of Carleton, the choice made for this book will seem unfortunate.

There is a foreword by Sir Roy Cameron which informs the reader that, "A pupil of Gustav Mann, whom he succeeded at Oxford, and of Champy, he inherited their common sense and uncanny intuition". Actually, Carleton never saw Mann, was not his pupil, and did not succeed him. Carleton was trained as a cytologist by the reviewer and succeeded the latter after he had migrated to University College, London. There seems little doubt that Sir Roy's kindly piece about "common sense and uncanny intuition" must have belonged to Carleton's period with C. Champy at Paris. J. Brontë Gatenby

TELECOMMUNICATION

Communication Engineering

By Dr. W. L. Everitt and Prof. G. E. Anner. Third edition. Pp. xi+644. (London: McGraw-Hill Publishing Company, Ltd., 1956.) 67*s.* 6*d.*

THE recognition of telecommunication as a separate and distinct branch of applied science involving fundamental principles of great generality and requiring powerful mathematical weapons for attack upon some of its problems may be said to have developed during the nineteen twenties. Prof. W. L. Everitt's text-book, when it first appeared in 1932, was one of a very small group of pioneer texts which exemplified this recognition and endeavoured to treat the subject of telecommunication as a unity. The book, which was written at a level appropriate to university undergraduate courses, was quickly accepted by teachers as a work of exceptional quality and before long had established itself as one of the standard text-books for students.

The third edition of "Communication Engineering" appears under the same title but under the joint authorship of Prof. Everitt and Prof. G. E. Anner. In the preface to the new edition the authors remark that, at the time at which the first edition was planned, it did not appear presumptuous to cover, in one volume, the major fundamental concepts in the field. Now, however, that is quite impracticable, and "it has been decided to concentrate on the area which must precede the study of all other divisions of communication, namely, the fundamentals of linear-network analysis and synthesis including the use of unilateral elements".

The book opens, as did its predecessor, with a chapter on the fundamental principles of communication networks. This introduction is excellent. The basic concepts underlying multi-channel frequency-division communication systems are introduced almost at once, and this is followed by a clear description of amplitude and angle modulation and of the relative effects of interference in the two systems. A similar treatment is given of the principles of signal sampling, pulse-modulation and time-division multiplex. Finally, there is a section dealing briefly with the quantitative measure of information and with the implications of the Hartley–Shannon law.

Two chapters are devoted to the transient and steady-state analysis of linear networks. These are followed by a chapter giving a thorough treatment of resonance and a chapter on bridge networks. This last chapter deals with the important applications of the bridge principle in communication circuits, namely anti-side tone, duplex and phantom circuits, two- and four-wire repeater circuits and circuits for the stabilization of radio-frequency amplifiers. The treatment of passive networks with lumped parameters is completed by two further chapters on iterative networks and wave filters. Transmission lines, in the new edition, occupy a good deal more space than in the old, there being a separate chapter on lines of low loss which includes a very satisfactory treatment of impedance charts and their applications. It is noteworthy that in addition to deriving the transmission line equations as the limiting case for a repeated lumped network these are also established from the fundamental differential equations. In my opinion Prof. Everitt's application of the compensation theorem to establish the steady-state relationships for mismatched termination and reflexion is a most valuable illustration of the power of circuit theory, but it lacks the quality of developing physical insight. The concept of a true time delay in transmission can be first developed unambiguously for the genuinely distributed system and then interpreted for the repeated lumped system satisfactorily, but the reverse sequence presents some awkward problems.

Impedance transformation receives very full and satisfactory treatment, excellent illustration being given of the use of the Smith chart in relation to broad-band impedance transformation. One chapter is devoted to equalization and includes a fairly full treatment of the semi-graphical method of computing the attenuation response curve which is known as the 'corner plot' method.

Two further chapters complete the main text of the book. The first of these treats linear amplifiers. Again the treatment is on as general a basis as is practicable, figure of merit being introduced at an early-stage, design for maximally flat response receiving considerable attention and the relations of steady-state response, transient response and amplitude response being studied. The final chapter, entitled "Electromechanical Coupling", gives a brief elementary treatment of the more important electromechanical transducers employed in telecommunication.

Comparing the new book with the old, there are inevitably losses as well as gains. Those like the present reviewer who had come to regard certain sections of the old book, as for example that on modulation and demodulation, as giving some of the clearest and most illuminating elementary treatments available, cannot but regret the disappearance of a good many well-tried and familiar sections. On the other hand, the more comprehensive treatment of linear communication networks on a 'broad-band' basis is of the highest value.

As a text for students the new edition of "Communication Engineering" is a work of excellent quality which should commend itself as did its predecessors to the good opinion of teachers of the subject.

James Greig

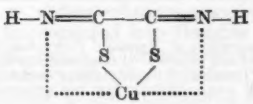
TIMBER PRESERVATION BY COPPER COMPOUNDS

By D. S. BELFORD and Prof. R. D. PRESTON, F.R.S.
Botany Department, University of Leeds
AND
C. D. COOK and E. H. NEVARD
Messrs. Hickson's Timber Impregnation Co. (G.B.), Ltd., Castleford

DURING the past year we have been making what is probably the first attempt to utilize modern physical techniques of sub-microscopic structural research to resolve some of the outstanding problems associated with the impregnation of timber by water-borne preservatives. The long-term object of the work is to determine why certain timbers are impermeable to preservatives, while others apparently of the same microscopic character can be treated with ease. In view, however, of the lack of information concerning the precise location of the ingredients comprising the preservatives within the timber, the immediate problem has concerned an investigation of the physical state and distribution of preservatives in the timber on a sub-microscopic scale. We have used the methods of polarization microscopy, X-ray diffraction analysis, electron microscopy and electron diffraction analysis. The results obtained to date seem to us to be of sufficient importance to merit immediate publication pending the preparation of a series of longer papers.

The work so far has been carried out exclusively on Douglas fir (*Pseudotsuga taxifolia*) for several reasons. Douglas fir is widely used in Great Britain for constructional purposes, but is often difficult to treat with preservatives. The heartwood is only moderately durable and the sapwood very liable to decay. Because of the lack of durability of the heartwood, long and expensive treatment schedules are frequently required, and even then the results are irregular and sometimes inadequate. A further advantage of Douglas fir as a test material is that, being a conifer, it has a relatively simple structure consisting only of two principal cell types—tracheids and ray parenchyma.

The preservative used for the main investigation was that known commercially as 'Tanalith' *C* (a mixture in water of copper sulphate, potassium dichromate and arsenic pentoxide); but in addition tests were also made with copper sulphate alone, copper sulphate/potassium dichromate mixtures, arsenic pentoxide alone, as well as copper arsenate, chromium arsenate, cobalt chloride, ferric chloride and zinc chloride. Each treatment was carried out on matched blocks measuring 2 in. × 2 in. × 1 in. Initially, blocks were treated under pressure, but the following treatment was finally adopted. The blocks were placed individually in a beaker and weighted with a lead weight, and the beaker was then placed in a desiccator under a vacuum of 27 in. of mercury for 10 min. The treatment solution was then admitted without allowing air to enter and the vacuum maintained for 10 min. longer. Air was then admitted to the desiccator and the timber allowed to soak for two hours, after which it was dried. Although the timber generally darkens on treatment, the coloration is too weak to allow determination of the distribution of the preservative in sections using the light microscope. Accordingly, various staining techniques were applied either before or after sectioning, and the most effective of these proved to be rubeanic acid (dithio-oxamide).



which under alkaline conditions forms a deep blue insoluble complex with trace amounts of copper. The microscopic appearance of the wood was then most revealing, two points in particular being very noticeable. First, in no conditions was any of the blue copper–dithio-oxamide complex observable in the cell lumina. This shows that the preservation of wood using a copper salt does not depend on the lining of the cell lumina with a copper compound. On the other hand, the middle lamella in particular was stained very deeply and the stain was noticeable throughout the whole of the cell-wall thickness. The stain was, however, patchy over any section, making it quite clear that the copper was not distributed uniformly throughout the test wood sample. The increased durability of the timber as a result of treatment with an aqueous solution of copper salt must therefore depend on the copper content of the cell walls and on the forms in which the copper is present.

Longitudinal sections stained with dithio-oxamide and examined under the polarizing microscope exhibited a spectacular dichroism. Apart from disturbances caused by the bordered pits, the sections were a deep blue colour for light vibrating in a plane parallel to tracheid length and pale yellow for light vibrating at right angles to tracheid length. Whenever, in a section, the cellulose microfibrils changed direction, the dichroism changed accordingly. These observations indicate that the copper–dithio-oxamide complex is orientated specifically with respect to the cellulose microfibrils. It must be concluded that at least a proportion of the copper in the cell wall is associated very closely with the cellulose.

This led us to examine impregnated wood in the electron microscope, using both ultra-thin sections and material ground in a blender. Ultra-thin sectioning of wood is notoriously difficult, and this is also true of preserved wood. Nevertheless, the sections we have been able to examine have shown, within the cell walls, the presence of sub-microscopic particles distributed at random (Fig. 1*b*). These particles were identical in appearance to some of the crystals which appeared when a drop of 'Tanalith' *C* solution was evaporated to dryness on a specimen carrier (Fig. 1*a*). There does appear, therefore, to be evidence that certain components of 'Tanalith' *C* are deposited at random within the cell wall.

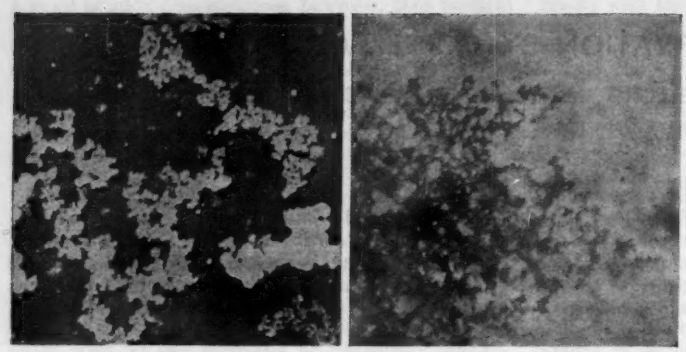


Fig. 1. (*a*) Micrograph of 'Tanalith' *C* crystals from a 0·5 per cent aqueous solution dried on to specimen support. Palladium/gold-shadowed. (× 19,800.) (*b*) Micrograph of a section of 'Tanalith' *C* impregnated *Pseudotsuga* late wood, showing crystals within the cell wall. Methacrylate not removed, unshadowed. (× 19,800)

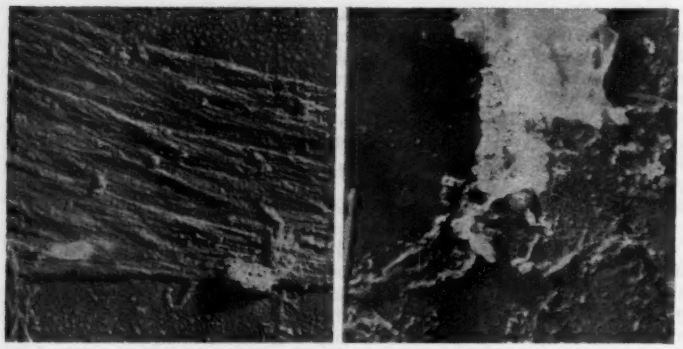


Fig. 2. (*a*) Micrograph of a particle of blended untreated *Pseudotsuga* wood. Palladium/gold-shadowed. (× 19,800.) (*b*) Micrograph of a particle of blended 'Tanalith' *C*-impregnated *Pseudotsuga* wood, showing aggregations of electron-dense preservative material. Palladium/gold-shadowed. (× 13,800)

When pieces of untreated wood, after disintegration in the blender, were examined in the electron microscope, the cellulose microfibrils appeared to be relatively free of opaque incrustations (Fig. 2*a*). The cellulose microfibrils of wood treated with 'Tanalith' *C*, however, showed heavy incrustations of some electron opaque material (Fig. 2*b*). Certain fragments of the treated wood, whether showing incrustations or not, gave remarkably sharp and characteristic electron diffraction diagrams (Figs. 3*a* and 3*b*). We have checked these diagrams against the diagrams of all the various components of 'Tanalith' *C* and, using the A.S.T.M. index of crystal spacings, against the X-ray diagrams of all known copper salts, without finding any agreement. The diagrams, however, resemble though are not identical with the X-ray patterns of the copper–alkali–cellulose II described by Hess and Trogus[1]. Furthermore, the electron diffraction diagrams faded fairly rapidly when the intensity of the electron beam was increased, a phenomenon which is characteristic of organic rather than of inorganic compounds. In every case the electron diffraction diagram is oriented with respect to the cellulose microfibrils. It seems, therefore, probable that at least a proportion of the copper within the cell walls occurs in the form of a copper–cellulose complex. The X-ray diagram of the whole of the treated wood failed to reveal the presence of this complex owing, no doubt, to the relatively small amount of copper which is present in the wood. This failure does, however, show further that the complexing is limited to strictly localized regions of the cellulose.

It has also been observed that similar diffraction patterns to that obtained for 'Tanalith' occurred when the wood was treated with aqueous solutions of copper sulphate and copper sulphate–potassium dichromate mixtures. Since the electron diffraction work has been purely qualitative, it has not been possible to assess whether there is a quantitative difference in the copper cellulose complex between treatments with 'Tanalith' *C* and treatments with copper sulphate alone. When the wood was impregnated with chromium, cobalt, ferric and zinc salts, similar diffraction diagrams were again obtained. It must be concluded from these observations that when timber is impregnated with metallic salts of the type described, the metal component is situated within the cell wall of the timber and a proportion at least is complexed with the cellulose to form metallo-cellulose complexes.

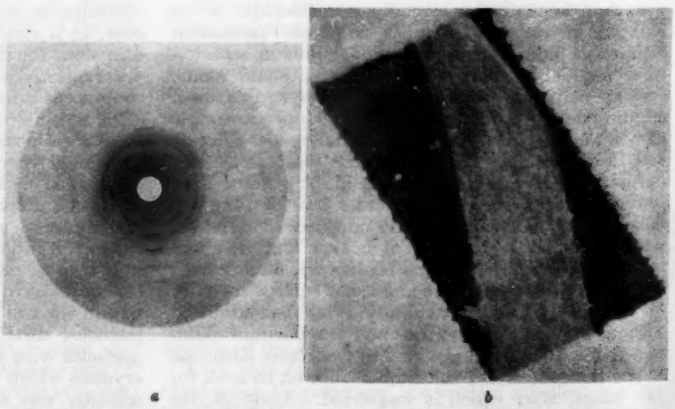


Fig. 3. (*a*) Electron diffraction diagram of the metallo-cellulose complex, given by the particle of cell-wall shown in Fig. 3*b*. The continuous rings are due to the palladium/gold-shadowing. (*b*) Micrograph of a particle of blended, 'Tanalith' *C*-impregnated *Pseudotsuga* wood, giving the electron diffraction pattern shown in Fig. 3*a*. Palladium/gold-shadowed. (× 4,450)

After completing the preliminary work described in this report, our attention was directed to the work of Walton-Smith *et al.*[2] on the preservation of timber, using copper formate. These workers have concluded from indirect evidence that, after impregnating the wood with copper formate followed by autoclaving, the copper is converted to a copper–cellulose complex and that it is this complex which confers upon the wood its durability. Our own results prove conclusively the existence of the complex, and, taking their results with ours, we can be rather specific concerning the location of this copper within the cellulose microfibrils.

Cellulose microfibrils consist of a number of molecular chains of cellulose lying parallel to each other and, over certain regions of the microfibril, regularly arranged in a space lattice. It is quite impossible to conceive that aqueous solutions containing copper ions could penetrate into these crystalline regions since water itself is known not to penetrate. These regions, however, are surrounded by others in which the cellulose is paracrystalline; the cellulose chains here lie approximately parallel to each other but are not regularly spaced. Within these regions the copper ions can penetrate, and it is in these areas of the microfibrils that we would expect the copper–cellulose complex to form.

Walton-Smith *et al.*[2] have found that the maximum amount of copper fixed within the wood using their copper formate method is about 0·8 per cent by weight of copper. This copper loading corresponds very roughly to 1 copper atom per 20 glucose residues within the paracrystalline regions of the microfibrils. It is clear that if this copper were distributed uniformly within the paracrystalline regions, a uniform space lattice would not develop and no electron diffraction diagrams of the copper–cellulose complex would be possible. The fact that electron diffraction diagrams are obtained shows quite clearly that the copper is located within the paracrystalline regions of the microfibrils, and within these regions sufficient copper is incorporated to link the cellulose chains laterally into an ordered space lattice.

We conclude, therefore, that the metallic components of a copper–chrome–arsenic water-borne preservative impregnated into Douglas fir are located within the cell wall. A proportion at least of this metal complexes with the cellulose of the paracrystalline regions of the microfibrils and the resulting metal–cellulose complex is highly orientated. We are not yet certain as to any connexion with this complex of the crystalline deposits observed in the electron microscope to be distributed at random within the walls.

[1] Trogus, C., and Hess, K., *Z. phys. Chem.*, **6**, No. 1, 1 (1929).
[2] Walton-Smith, F. G., Bottoms, R. R., Abrams, E., and Miller, S. M., *Forest Prod. J.*, **6**, No. 9, 340 (1956).

PHOTOSYNTHESIS

A SYMPOSIUM on photosynthesis occupied the morning session, on September 10, of Section K (Botany) during the recent Dublin meeting of the British Association. Prof. W. Stiles was in the chair.

Dr. G. E. Fogg, of University College, London, opened the symposium with a paper on "Actual and Potential Yields in Photosynthesis". He said that the total energy reaching the Earth's surface was 5×10^{23} calories a year; at present the most effective conversion of this to potential energy is by green plants in photosynthesis. Schroeder's estimate of the total yield of photosynthesis on Earth, particularly of the yield of forests, namely, $1{\cdot}63 \times 10^{10}$ tons of carbon per year, was probably too small. An estimate of the forest production based on the most recent information was $1{\cdot}54 \times 10^{10}$ tons per year (instead of $1{\cdot}10 \times 10^{10}$), giving a revised total world production of $2{\cdot}1 \times 10^{10}$ (or $2{\cdot}4 \times 10^{10}$ if respiratory losses were allowed for). There is still uncertainty as to the total production in the oceans. Using the radiocarbon method, Steemann Nielsen recently found an average value for tropical and sub-tropical waters of between 0·1 and 0·2 gm. carbon/m.^{2}/day. Other workers have found somewhat higher values, suggesting a total production for the whole hydrosphere of $3{\cdot}2 \times 10^{10}$ tons per year. This is considerably less than some earlier estimates. One difficulty is to decide whether the radiocarbon method measures net or gross production: further error will arise if any of the products of photosynthesis are excreted from the plant. The value of $3{\cdot}2 \times 10^{10}$ is to be regarded as a firm lower limit and in fact may be too small by a factor of up to five.

If the radiation of utilizable wave-lengths alone is considered, then a total yearly production of $5{\cdot}6 \times 10^{10}$ tons corresponds to an efficiency of energy conversion over the Earth's surface as a whole of approximately 0·2 per cent. Under optimal conditions of low light intensity in the laboratory, efficiencies of 25 per cent and greater have been obtained. In part, the efficiency in the field is lower because the intensity of sunlight is too high for efficient conversion by the plant. To obtain higher values under natural conditions it is necessary to find new varieties or new crop plants which are capable of utilizing efficiently the natural radiation and then seek methods of using their produce. An ideal crop plant would have a complete ground-cover throughout the growing season, continuously producing new leaves and allowing a continual harvesting of leaves after they had passed their maximum activity. Alternatively, unicellular algae offer the possibility of higher yields, but these must be grown in tanks specially designed to obtain maximal utilization of light energy. In this case, sewage can be used as a source of carbon dioxide. Yields up to 34 gm. carbon/m.^{2}/day have been obtained in small-scale trials. The price of the product is likely to be five to ten times that of conventional crops, and Dr. Fogg concluded that the process is unlikely to be economically possible in the near future unless some radical simplification in technique is achieved.

Dr. C. P. Whittingham, of the Botany School, University of Cambridge, spoke next on "The Chemical Nature of Photosynthesis". He began by discussing the work of Calvin and his colleagues who, by combining the techniques of paper chromato-

graphy and tracer carbon, were able to make great advances in our knowledge of the biochemistry of photosynthesis. Two types of experiment gave information as to the intermediates between carbon dioxide and carbohydrate. First, the percentage activity of a compound as a fraction of the total radioactivity fixed was determined, and the first-formed intermediate assumed to be that which, at zero time, would extrapolate to 100 per cent. This type of experiment indicated that phosphoglyceric acid was the compound first formed from carbon dioxide. Secondly, evidence was obtained by determining the relative activity of individual carbon atoms in the labelled molecules. The first-formed phosphoglyceric acid and hexose were labelled exclusively in the third and the third and fourth carbon atoms, respectively, indicating a two-carbon precursor. In fact, the two-carbon compound postulated turned out to be a five-carbon molecule, ribulose diphosphate. In light, phosphoglyceric acid is believed to be reduced to triose and hence to carbohydrate; in addition, some triose and hexose are converted via sedoheptulose to re-form more ribulose, which then continues the reaction sequence. A continuous supply of two reagents is required to operate the cycle in the direction of net synthesis: a supply of reducing power and of adenosine triphosphate. Both must be produced as a result of the absorption of light energy.

Previous to work with carbon isotopes, a physical separation of the process of carbon reduction from that of the fixation of light energy had been achieved by Hill using chloroplasts isolated from the plant. As then prepared, isolated chloroplasts showed no reaction with carbon dioxide, but were able, in light, to reduce ferric salts, quinone and other substances. It is possible that in the plant, reoxidation of part of the reduced product via a suitable enzyme system could result in the formation of adenosine triphosphate, thus supplying both requirements of the carbon cycle. Dr. Whittingham suggested that those cytochromes which are known to occur only in photosynthetic tissues might be concerned in this phosphorylation which depends on light. Isolated chloroplasts, suitably prepared, have more recently been shown both to phosphorylate suitable acceptors in the light and to be also capable of carbon dioxide reduction. Thus any spatial separation of the photochemical and thermochemical processes in photosynthesis is not at the gross morphological level of plastid and cytoplasm.

Attempts have recently been made to study the structure of the chloroplast and relate it to its photochemical activity. The electron microscope has revealed a multi-layered structure with areas of a high degree of organization, tentatively identified with the 'grana' seen in the light microscope. Mercer and his colleagues in Australia have studied the change in structure occurring during greening of etiolated maize seedlings. In the etiolated plant the chloroplasts had an irregular granular appearance, but as greening occurred the development and organization of a layered structure were observed concomitant with the development of photosynthetic activity. The extensive interfacial area produced by a multi-layered structure offers a surface suitable for the orientation of chlorophyll molecules. This would result in a concentration of pigment within the interface, thus facilitating energy transfer both between accessory pigment molecules and between chlorophyll molecules. Tentative calculations show a permissible transfer of excitation energy from an absorbing molecule through several hundred other molecules before dissipation. Long ago, Emerson and Arnold showed that not every chlorophyll molecule, but about only one in every five hundred, was capable of producing oxygen from a brief intense light flash. This would be consistent with a unit of 500–1,000 chlorophyll molecules associated with each energy conversion centre. Such a unit is much smaller than the chloroplast or the granum and might be identified with a portion of lamellar interface. The nature of the energy conversion centre at which excitation energy is converted to chemical bond energy is still not clear. Some consider it to be an enzymic link between intermediates of the carbon path and certain individual chlorophyll molecules. Others favour the view that it is a physical structure with polar character analogous to a *p–n* junction. Excitation results in a supply of electrons to one surface and depletion from the other; the electrons and 'positive holes' then initiate respectively the carbon reduction process and oxidation of water to molecular oxygen.

The final paper was by Dr. S. R. Elsden, University of Sheffield, who spoke on "The Photosynthetic Bacteria". Photosynthesis in all three major groups, the Chlorobacteriaceae, the Thiorhodaceae and Athiorhodaceae, differs from that in the green plant in that no oxygen is produced and an additional substrate—more or less specific to the group—is required. Nevertheless, there are a number of features common to photosynthesis in bacteria and the green plant.

All three groups of bacteria contain both chlorophyll and carotenoid pigments and these are located in small spherical particles, the chromatophores. The chlorophyll of the Chlorobacteriaceae appears to be very closely related to the chlorophyll *a* of the green plant; the Thiorhodaceae and Athiorhodaceae have a different chlorophyll which is a tetrahydroporphin derivative. The action spectra for growth and for photosynthesis are similar to the *in vivo* absorption spectrum of the chlorophylls, indicating that the chlorophylls are the primary photosynthetic pigments as in green plants.

The Thiorhodaceae can use as substrate hydrogen, sulphur compounds and a wide range of organic compounds; the Athiorhodaceae can use hydrogen and organic compounds but not sulphur compounds. With organic substrates most of the substrate carbon is converted to cell substance, but in addition carbon dioxide is taken up if the substrate is more reduced than carbohydrate and given out if more oxidized. This has made it difficult to determine the amount of carbon dioxide fixation. Attempts to use carbon-14 dioxide have been complicated, due to the presence of exchange reactions. Inhibition by cyanide is greater where a substrate is metabolized with the fixation of more carbon dioxide. It appears probable that the process of carbon dioxide fixation in the bacteria is similar to that in the green plant.

Specific cytochromes have been found in the photosynthetic bacteria and are presumed to play a similar part to that of the cytochromes found associated with the chloroplast of the green plant. The bacterial cytochromes are of the *c* class with absorption maxima for the α-band between 550–555 mμ. They are not autoxidizable and differ in oxidation-reduction potential from organism to organism, varying, for example, from − 100 mV. for

a compound isolated from the green bacterium *Chlorobium thiosulphatophilum* to + 340 mV. for a compound from *Rhodospirillum rubrum*. Duysens and Chance and Smith have shown by studies of difference spectra that a hæm pigment is relatively oxidized in light and reduced in dark in *Rhodospirillum rubrum*. Illumination of preparations of chromatophores isolated from the bacterium is accompanied by phosphorylation of adenosine phosphate, and it is probable that this is related to the oxidation of hæm pigment observed in light. This would indicate a close similarity in the photochemical activity of chloroplasts isolated from the green plant and chromatophores isolated from the photosynthetic bacteria.

The elucidation of the reactions involving carbon dioxide using isotopes and the comparative studies of photosynthesis in bacteria and green plants emphasize that the basic biochemical pattern is essentially similar to that of the dark metabolism of other organisms, both plant and animal. The unique feature of photosynthesis lies in the mechanism whereby light energy is used to drive the reaction sequence in the direction of net synthesis. An understanding of the mechanism of energy conversion is the major challenge for future research in photosynthesis and may contribute to the technology of energy conversion just as the study of the over-all process of photosynthesis has to the technology of food production.

C. P. WHITTINGHAM

A TRIBUTE TO FREDERICK SODDY*

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THE first International Conference on Radioisotopes in Scientific Research seems an appropriate occasion upon which to consider our debt to Frederick Soddy. The duty to clarify his picture is specially incumbent on us, as it is the tragedy of his life that members of the younger generation may know him only as the person who adopted the term 'isotope' and, perhaps, as the author of provocative statements in economics and other fields far remote from science. The number of those who knew Soddy in his creative period is dwindling.

In fact, the whole science of radioactivity owes to Soddy infinitely more than the coining of the household word which is the unifying tie of this Conference.

First, I would like to recall that the fundamental theory of radioactive disintegration was developed by Rutherford and Soddy. From experiments carried out during 1901–3 at the University of Montreal by the physicist Rutherford and the chemist Soddy, they drew the conclusion that the emission of the Becquerel-rays (as they were called in those days) was accompanied by chemical transmutations; in a vague way such a hypothesis had been considered before as one of several possibilities, but the French school in particular had favoured other explanations. Anybody who studies the original papers will easily recognize the decisive part the chemist must have played in this joint work; some of the arrangements are, from the point of view of experimental chemistry, models of a scientific investigation. Nevertheless, in later books Soddy's name sometimes no longer appears in this context: to Rutherford is attributed the sole merit—illustrating the old truth, well known to students of the history of science, that great reputations tend to absorb the smaller ones—although Rutherford himself always gave full credit to his colleague.

Their ways, however, soon parted. Soddy's name immediately appeared again in connexion with an experiment of the greatest significance: the proof that, in the process of radioactive disintegration by α-rays, helium is evolved in sufficient quantities to be identified spectroscopically. This time the team was Ramsay and Soddy: the study of such small quantities of rare gases is so difficult that in those days Ramsay's laboratory in London was the only place where the necessary experience was available, but the radioactive technique—then quite new to Ramsay—was clearly Soddy's contribution. Anybody who knows from Ramsay's later publications on radioactive transmutation, after Soddy had left, how incapable he was of taking the precautions necessary in this field will credit Soddy with the clean and convincing conduct of experiments in which he later proved himself so much more adept than Ramsay.

So far, Soddy's name had been linked with those of senior and already very famous investigators. He came fully into his own during the ten-year tenure of a lectureship in physical chemistry at the University of Glasgow, where he devoted himself to radiochemistry proper, that is, to the study of the chemical behaviour of the radioactive substances. Such work had been going on in many laboratories, but the published results were frequently erroneous and no attempt had been made at a comprehensive survey. By far the clearest presentation of the new subject was given by Soddy in 1911, in a small volume called "The Chemistry of the Radioelements". Here, for the first time, the phenomenon of the chemical inseparability of those substances which to-day we call isotopic was stressed as something fundamentally new and important. More than that, a connexion was indicated between the position that a radioelement occupies in the disintegration series and in the periodic table; the first part of the important 'radioactive displacement law' is already contained in this book, namely, the rule that emission of an α-particle means shifting down by two places in the periodic table. The second part of the law, namely, that emission of a β-particle leads to the production of an element one place higher in the table, was pronounced three years later, almost simultaneously, by Fajans and Soddy; the experimental basis for this statement had in the meantime been safely laid, largely through the systematic efforts of Soddy's laboratory. In the course of various researches the inseparability of some radioelements from other elements had independently been found by Svedberg, by Boltwood, by Hahn and others, but it is Soddy's outstanding merit to have undertaken a special

* Address delivered in Paris on September 9 at the inaugural session of the International Conference on Radioisotopes in Scientific Research.

investigation in order to clarify this mysterious phenomenon; here he was ably helped by a Scottish student with the name of A. Fleck, now Sir Alexander Fleck, chairman of Imperial Chemical Industries, Ltd. Their well-planned analytical work contributed decisively to the recognition of the validity of the displacement law and thereby to the understanding of the physical cause of isotopy. It was fitting that Soddy should christen this phenomenon, and that, in 1921, he should be awarded a Nobel Prize.

After these brilliant successes in his scientific efforts—I have not time to mention other excellent papers by Soddy—everybody would have expected him to become the leader of a strong British school of radiochemistry, in a position perhaps similar to that of Rutherford on the side of physics. Soddy's books ("The Interpretation of Radium" and others) were eagerly read; they showed didactic and literary qualities of the highest order and seemed to add to his qualifications for a successful teaching career. But nothing of this sort happened. True, after a few years at Aberdeen, Soddy was called to Oxford as professor of inorganic and physical chemistry, but little scientific work emerged from his laboratory there, no school of radiochemistry was formed, and in 1936 he gave up his chair and retired into private life. How is this surprising eclipse of Soddy as a scientific worker to be explained? To help us understand it, something must be said about his character.

Science was never the only concern in Soddy's life. He had a deep interest in social questions, and whenever he suspected that injustice was being done to a certain group, or that something was wrong in the social structure, he fought it in the most uncompromising way. I had an opportunity to see this side of his nature as early as 1913 when I had the privilege of learning the then current methods of gas microanalysis under his guidance in Glasgow. Scottish Sundays would have left me rather lonely if Soddy had not introduced me to the hospitable house of his parents-in-law, Dr. and Mrs. Beilby. Incidentally, I read recently in the *Proceedings of the Chemical Society* that on that house a tablet is to be fixed, recalling that there, about 1912, the name 'isotope' was invented. This date is certainly too early; in the many discussions to which I had the pleasure of listening in the first half of 1913, this word was never used. According to Soddy's own story, it was a little later supplied to him by a school teacher, a lady to whom he had explained that the substances to be named occupied "the same place" in the periodic table. (The term made its first public appearance in Soddy's letter to *Nature* of December 4, 1913, p. 399.) It is very unfortunate that in recent years this clear scientific meaning has been obscured by the indiscriminate use of the word 'isotope' for any radioactive substance. If no relation to another substance occupying the same place is involved, the designation 'radioelement' or 'radionuclide' ought to be used. One substance in isolation can no more claim to be an isotope than an only child can be a brother.

I remember very clearly having heard Soddy's heated arguments, in Dr. Beilby's house at 11 University Gardens, in favour of home rule for Ireland and votes for women, the two main political topics of those days. Later he took a deep interest in political economy; to the theory of money he devoted several publications in which he expressed very radical views. Objections from acknowledged experts in this field he used to brush aside with the remark that chemical experts did not accept his views on isotopes either when he first pronounced them. There was, however, the difference that in chemistry he could present such convincing facts that resistance was overcome within a few years. In economics he met with no such success, and he became more and more embittered about this failure.

Nearer home, he tried to introduce reforms into the structure of the University of Oxford; he considered some aspects of the college system, as, for example, the independent teaching of physical chemistry in several small and poorly equipped college laboratories, as outmoded. He was a declared admirer of some features of the German university system. However, he was not good at waiting or satisfied with slow progress, but was always inclined to suspect unpardonable indolence or even ill-will. After he had left Oxford some developments went in the direction desired by him, just as votes were given to women and independence to Ireland. But Soddy did not wait. Never satisfied by a compromise, he manœuvred himself more and more into the position of an opponent and critic without influence; finally he resigned, and Britain lost the hope many had certainly cherished that this great man and his pupils would establish a permanent school of radiochemistry.

After his retirement, Soddy had little contact with colleagues and followed the further development of the science he had helped so much to launch with growing distrust. He resented especially the dominant role physics assumed in radioactive research. Apart from the general trend—physics has invaded other branches of chemistry as well—it was Soddy's own premature retirement which accelerated this shifting of the centre of gravity. He had been the only man in Great Britain who could to a certain extent have kept the balance. Instead he was, in his later years, inclined to believe in dark scheming on the part of physicists who did not want to acknowledge the merits of chemists. But anybody who ever had the opportunity of knowing the generous character of Rutherford and his readiness to admire and enjoy good scientific work, wherever it was done, will be quite unable to accept Soddy's occasional bitter remarks. It is most regrettable that these unfounded grievances of an old and disgruntled Soddy have found their way into recent books.

The reasons for Soddy's tragic scientific isolation in later years are to be found in his own personality. He was gifted in many, perhaps too many, ways. He was such a good writer of English prose that it was all too easy for him to give his polemical essays the sting he wished. Once, when he had solved a problem of stereometry, it amused him to publish it in verse. An occasional excursion into the history of chemistry instigated him to the best vindication known to me of the strong claims of William Higgins, as opposed to those of John Dalton, to be the originator of the chemical atomic theory. His special gift for technical constructions made him for long periods exchange the laboratory for the workshop. There are many other examples which could be quoted to illustrate the richness and variety of his talents.

Rutherford once said in a lecture that he was naturally in favour of simple explanations in physics, being a simple person himself. Now, Frederick Soddy was not a simple person. He was a very complex personality, not easy to approach, living a rather solitary life—especially after the early death of his charming and devoted wife—but he was a great

idealist, always ready to fight against what he deemed morally wrong, without any consideration of his own personal interests. Very kind and helpful to young and struggling people, he was suspicious of nearly everyone in authority and power. If he had lived, on September 2, 1957, he would have completed his eightieth year. It is fitting, at a conference to discuss the scientific applications of isotopes, to remember the man who was the first to see the general theoretical importance of what had been until then scattered observations. Let us honour the memory of a brilliant intellect, an experimenter second to none among the founders of radiochemistry, and an uncompromising champion of his ideals.

OPERATIONAL RESEARCH

IT is just about twenty years since the expression 'operational research' was coined to describe the activities of the Air Ministry research section studying the operational problems of radar. There was rapid progress during the first decade, mainly—and quite naturally—in military applications. The three British Armed Services all had groups in England, and there were many overseas sections. In the United States and Canada development was also rapid, and a tripartite operational research conference on defence matters was held shortly after the War; similar conferences have since been held at regular intervals, and have been extended in the military sphere to include nations of the British Commonwealth and the North Atlantic Treaty Organization.

Although work of the type now termed operational research has been carried out in industry for the best part of a hundred years, it is only since 1947 that there has been any formal description of this science. An Operational Research Society was founded in the United Kingdom in 1947—initially as a club with members drawn from personnel of the various military groups who had returned to civilian life. An American Society was formed in 1953 and a year or so later came the (American) Institute of Management Science. Societies or groups have since been formed in most of the major Western European countries, and also in India and Japan.

With this widespread interest, it is understandable that suggestions for an international meeting this year met with a ready response. Indeed, this highly successful conference (sponsored by the Operational Research Societies of Britain and America and the Institute of Management Science) for experienced workers in both the military and civil fields was over-subscribed from the start. The Conference was held at Oxford during September 2–6, and the two hundred and fifty members present represented twenty-one different nations, and it was felt that similar conferences should now be held at regular intervals.

At the inaugural meeting delegates were welcomed by Sir William Slater (president of the Operational Research Society). The eminent speakers who followed him avoided any attempt at formal definition of operational research, but spoke with great authority on its basic principles and growing importance in industry, in defence and in the economy of nations. The first four business sessions were devoted to the presentation of papers on methodology and applications, and the final session to development (that is, to the extent of growth of operational research) in the main countries represented. During the week, one session was spent in panel meetings, at which were discussed special aspects of operational research, for example, education and training, or its relation to management. There were a formal dinner and reception on the first night and also informal meetings during the week; these latter were prosecuted so vigorously that it is doubtful if any delegate got his or her full ration of sleep during the conference. After leaving Oxford, parties visited various British operational research centres. The proceedings of the conference are to be published at the end of the year and can be obtained from the *Operational Research Quarterly* (11 Park Lane, London, W.1).

The largest delegations were from Britain and the United States, and these accounted for twenty-four of the twenty-eight main papers. The conference brought out differences in the approach of these countries to operational research. Judging by the papers presented, interest in the United States is greater in development of mathematical techniques (seven papers) than in applications (three papers), though the methodological papers were usually based on real situations involving decision-making. This mathematical interest seems to stem from universities and research organizations. In the United States much operational research is conducted on a consulting basis by university departments, and this no doubt stimulates academic research. In the United Kingdom, however, interest is in applications (six papers) rather than methods (three papers). It is lamentable that so few British universities show any real interest in operational research. There are many individual workers known by their publications, but some of these are not members of the Operational Research Society and so were not eligible to attend this conference.

If papers are to be judged both by reading and by the interest aroused, then there were outstanding contributions in each session. On the morning of September 3, Mr. H. K. Weiss, of Northrop Aircraft, Inc., presented a paper on "Lanchester-type Models of Warfare". F. W. Lanchester's differential equations are well known from his classical work, "Aircraft in Warfare: The Dawn of the Fourth Arm" (Constable, London, 1916). In Weiss's paper historical data were used to establish the reasonableness of the Lanchester assumptions and then to expand the theory to take into account the movement of forces. It then deals with small combat forces, weapons of greatest effectiveness, and combat between heterogeneous forces. This work all leads to development of optimum tactics between heterogeneous forces. In the discussion it was acknowledged that the simplifying assumptions and unknown values of the relative effectiveness of weapons (killing-rate) cause serious difficulties. It is doubtful, for example, whether the effectiveness of a force is equal to (numerical strength) × (weapon effectiveness), for this assumes that a man who can and should shoot will in fact do so. Another complication is overhitting: a casualty may be due to more than one

hit, each of which is sufficient to incapacitate. For most weapons, however, the probability of hitting with a single shot (or even burst) is very low, and so overhitting is not initially important. In the case of a small force faced by much larger forces and in process of total elimination, overhitting may become substantial but it will not affect the outcome.

One other paper in this session should be of interest to the British public. It was a description by Messrs. J. Stringer (Central Electricity Authority) and K. B. Haley (University of Birmingham) of work in hand to reduce the cost of transport of coal to power stations to a minimum. The use of linear programming showed how some saving in cost of transport might be achieved. The effect of the loss of this business on another nationalized concern was not discussed. This paper also contained an account of an interesting mechanical analogue computer for solving linear programmes.

The afternoon session on September 3 was even more mathematical than that in the morning. The papers by Mr. T. C. Koopmans (Cowles Foundation for Research in Economics) on water-storage policy, and by Dr. R. M. Oliver (Broadview Research, Inc.) on control of production and inventories both contained much of mathematical interest. Comment on both, however, referred to the assumptions made in the mathematical model rather than to the mathematics itself. Mr. Koopmans's paper is of interest to those who heard the papers presented at a recent Royal Statistical Society meeting on queues.

Dr. J. H. Engel (Operations Evaluations Group, United States Navy) aroused more general interest with his paper, "Use of Clustering in Mineralogical and Other Surveys". His presentation, too, was much to be commended for its clarity and precision. In any search the first run will produce some spurious results and some misses. Further rapid runs will produce similar effects but will tend to confirm genuine signals. Such confirmed signals will then be the basis for more detailed examinations of areas in which prizes may be found. New fast searches are cheap, and detailed searches are expensive. It is likely that there is an optimum balance between effort on fast searches and detailed examinations giving maximum result per unit of expenditure. The paper read was confined to a special case in which the number of prizes in the area is known. A hypothetical numerical example given as an appendix to the paper illustrates the salient points. An (n,s)-clustering technique implies n coverings by fast search and a cluster of s contacts as the minimum required to justify detailed ground search. As in many other operational research studies, the answer is sensitive to the criterion. Applications of this theory do require accurate knowledge of equipment performance and costs, which are both matters of some difficulty.

The first session devoted to applications of operational research produced two papers of great general interest. All sufferers from traffic jams in Britain must be grateful for work on traffic flow. Mr. J. G. Wardrop (Road Research Laboratory) gave a paper on the "Traffic Capacity of Weaving Sections of Roundabouts". This described experimental work and its validation by observation of actual traffic conditions. The experiments were made at Northolt Airport during 1955–56, and some of the experiments were presented in film form. The main conclusion was that, in good conditions, about 800 mixed vehicles per hour per ten feet of weaving width can pass through a roundabout of normal design. Cycles, darkness and wet weather all reduce flow. Police control, however, appears to expedite matters. Much smaller flows may be encountered in some circumstances, as when two main streams meet and both turn right. Interference from adjacent roundabouts would also cause reduction. If this work is used as a guide to roundabout design much benefit should result. This type of analysis could be extended to show when roundabouts should be abandoned in favour of fly-overs, clover-leaf junctions and so on.

The other paper of particular public interest in this session was that by Messrs. J. C. R. Clapham and H. D. Dunn (National Coal Board) on communications in collieries. This attracted headlines in the daily press. In brief, underground communication in collieries was found to be inadequate for safety warnings and the cost of satisfactory improvement, on a national scale, is estimated at £5,000,000. Amortized over a reasonable period, this looks like only a few pence per ton on the price of coal—a very small premium for the safety of the men involved.

The second session on applications of operational research contained one paper that produced a long stream of commentators. This was on the "Level of Protection afforded by Stocks", by Messrs. John Harling and M. J. Bramson, of ORbit, Ltd. Stock control is a management function particularly susceptible to mathematical study and has, at one time or another, attracted the attention of many operational research workers. In the simplest terms, the object of this paper is to show the level of protection against run out of various levels of stock when the supply and demand functions to and from the stock are known. In this case delivery times were normally distributed, whereas demand from a production line was Poissonian. Cost of running out, that is to say, of stopping the production line, was not readily calculable. This paper represents an advance on previous published work in that it takes into account vagaries of delivery. Most stock control assumes constant lead time from order to delivery—and indeed delivery at fixed times is not unusual. However, circumstances can arise when vagaries of delivery are the main contribution to size of stock for a particular level of production.

The last paper of the session was by Mr. J. K. W. Slater (National Institute of Agricultural Engineering) on "The Collection of Data on the use of Machinery on Farms". This could well prove to be one of the main foundations of a study of how British farm productivity can be raised. It shows the dimensions of the problem clearly. For example, the average size of farm in England and Wales is only about 100 acres. More than 20 per cent of farms are less than 5 acres, though many of these very small farms must be exceptional in equipment and intensity of operation. Any idea of heavy investment on small farms (say, 100 acres) is likely to be ruled out on economic grounds, particularly in hill regions. Is it too much to hope that more thought will be devoted to understanding the problems of these farmers?

Looking back after a week or so, this conference seems particularly satisfactory for the international unity achieved. By the end of the week national delegations had fused most successfully and happily with one another. The feeling of common aims towards progress transcends everything else.

K. Pennycuick

AUTOMATIC DIGITAL CALCULATORS

A RETROSPECT*

By Dr. ANDREW D. BOOTH

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IT is now more than ten years since general-purpose digital computers became a subject of everyday discussion among scientists, and it is appropriate to look at the field to see if their early promise has been fulfilled. There is no need to discuss the structure of these machines, which are familiar to any research worker who has to use numerical processes in order to obtain his results or to predict from his theories; it suffices to say that the computer consists of five units, namely, arithmetical, control, storage, input and output.

The progress of the machines themselves over the past decade is not without interest. All the more elegant designs are derived from the classical work of the late John von Neumann[1], and it is unfortunate that he was promoted to the higher spheres of scientific administration before the Princeton machine was in a state in which he could use it extensively. Von Neumann, in common with all the other pioneers in the design of computers, under-estimated the difficulty of producing a reliable store of large capacity, and so the devices, which should have been operating in 1948, did not start to come into use until the early 1950's.

Four of the earliest machines to operate were built in England, namely, ACE, APERC, EDSAC, and MUEC[2]. All were taken up commercially, but it is sad to observe that technological virtuosity has allowed the Americans, in this as in so many other things, to overtake the British. The blame for this can be laid at the door of the manufacturers of electronic components: in 1947, I was forced to obtain miniature electronic valves from the United States; only in the past few years have reliable semi-conductor diodes been available in Britain, and the junction transistor is still far behind those available in the United States. Rectangular hysteresis-loop magnetic materials are but recently in quantity production, and it is perhaps symbolic that one large manufacturer assured me in 1950 that such devices were theoretically impossible, notwithstanding the fact that several American specimens were under test in his laboratory.

Coming now to the applications to which computers have been put, the field can be divided into four parts, comprising commercial, engineering, scientific and non-numerical uses.

Of the first class of applications little need be said. It is of comparatively recent origin, probably because such functions as wages calculation and tax estimation must be performed accurately and to a rigid time-schedule. No interest is attached to calculations of this type, which are trivial in concept and mathematics. More interesting, however, are some applications of computers to the planning of buying[3] and manufacturing strategy in business. Unfortunately, in its general aspect, this class of problem requires a storage capacity which is greater than that currently available, so that although small-scale test analyses have been carried out, no large-scale planning is in operation.

In engineering a number of interesting applications have been made, including the design of a proton synchrotron[4], non-linear control systems[5], power distribution network performance[6], power transformer design[7], the optimization of train schedules[8], and the analysis of frameworks[9]. The power-transformer design programme operates as follows. It is assumed that the machine is supplied with purchasers' specifications and with an initial estimate of the core area for the desired transformer. The machine calculates the number of turns on the low-voltage winding from the well-known formula: $N = k_1 V / k_0 A B f$, where k_1 is a scaling constant, V is the voltage applied to the winding, k_0 is the core space factor, A is the assumed core area, B is the assumed working flux density, and f is the operating frequency.

In general, N will not be a whole number, so that the machine has to take the nearest integer to it and re-calculate the flux density. On the basis of this integer approximation to N, the number of turns on the high-voltage winding can be evaluated by using the known transformation ratio specified by the customer.

Once these basic quantities are known, the next step is the calculation, from the known conductor sizes, of the window dimensions of the laminations; this is followed by an estimation of the weight of active iron, W, in the core.

At this point the first cycle of the design process is complete and the next stage is to estimate the excellence (or otherwise) of the result. The criteria are (1) iron loss, derived from the formula: $P = W(a_1 B + a_2 B^2 + a_3 B^3 + a_4 B^4)$, where $a_1 \ldots a_4$ are known loss coefficients; (2) load loss, Q, derived from currents and winding sizes and lengths; and (3) reactance, R. The quantities P, Q and R are then compared with the values which they require to have in order to meet the specification, and if necessary the core area, A, assumed initially, is modified by means of the formula:

$$\Delta A = A(\alpha \Delta P/P_d + \beta \Delta Q/Q_d + \gamma \Delta R/R_d)$$

Here α, β and γ are weighting constants, chosen as a result of experience to ensure optimum convergence. P_d, A_d and R_d are the customer's specified values of P, Q and R, and $\Delta P = P - P_d$, $\Delta Q = Q - Q_d$, $\Delta R = R - R_d$.

As soon as satisfactory values for the loss functions have been obtained, a final set of residual characteristics is evaluated and from this, if necessary, modifications are made to such preset parameters as the core material and the winding type and layout.

* Substance of a lecture delivered to Section G (Engineering) of the British Association in Dublin on September 10.

Finally, the machine calculates the arrangement of windings and core, costs, size of tank and so on, ending with an overall check to ensure that no mistakes have crept in. It is interesting to note that about three cycles of refinement are usually required to bring the losses within ± 2 per cent of those specified, and that the whole process can be completed in about four seconds on a medium-speed computer.

Space does not permit a description of the electric-traction programme, which is of considerable interest since it involves operations with discontinuous quantities, such as the sudden imposition of speed restrictions and the change of motor connexions with increase of speed. The value of this type of investigation is shown, however, by the fact that it indicated how, by optimum running, the energy consumption on the 40-mile run from Liverpool Street to Shenfield and back could be reduced by 40 per cent with a corresponding rise of only 14½ per cent in running time.

A half-way house between engineering and pure science is meteorology. Here, the methods of mathematical weather prediction pioneered by Brunt[10] are about to become practicably useful because the latest high-speed computers will enable the calculations to be performed sufficiently ahead of real time to qualify as predictions rather than verifications.

New scientific applications of digital computing machines appear daily and range from the study of stellar evolution to the binding energies of molecules, and from the design of optical systems to the analysis of speech. Since a mere catalogue would be uninteresting, a single example, from the field most familiar to me, will be considered in rather more detail. It is of topical interest because the recent determination of the structure of vitamin B_{12} by Dorothy Crowfoot Hodgkin[11] is a landmark in the analysis of molecular structure by X-rays and would have been impossible without an automatic digital computer.

In X-ray crystallography the basic data are a set of observed 'structure factor amplitudes', $|F_o(h,k,l)|$, which are simply related to the intensities of the X-ray reflexions which are obtained during diffraction measurements on single crystals. The Miller indices (h,k,l) are simple whole numbers.

It was shown by the Braggs that crystals could be considered to be built up of a large number of elementary building blocks—or unit cells—each of which is an identical copy of the others. Under these conditions the structure can be considered to be periodic, so that a Fourier expansion should be possible for the expression of variations in electron density from cell to cell. It can be shown[12] that, if the unit cell is assumed to have axial dimensions (a,b,c) and if (x,y,z) are the co-ordinates of any point inside that cell, then the density of electrons $\rho(x,y,z)$ is given by the triple Fourier series :

$$\rho(x,y,z) = \frac{1}{V}\sum_{h,k,l=-\infty}^{+\infty}\sum\sum |F_o(h,k,l)| \cos\left\{2\pi\left(\frac{hx}{a}+\frac{ky}{b}+\frac{lz}{c}\right)-\alpha_{h,k,l}\right\} \quad (1)$$

In this expression V is the volume of the unit cell and $\alpha_{h,k,l}$ is a phase angle which cannot, in general, be determined experimentally. If $\alpha_{h,k,l}$ were determinable from experiment a direct calculation of $\rho(x,y,z)$ could be made since the $|F_o(h,k,l)|$ are known; the calculations, though tedious, would then be well within the range of human computers. In practice, however, an indirect approach must be adopted.

It may be shown that :

$$F^2(h,k,l) = A^2 + B^2$$

$$\text{where } A = \sum_{r=1}^{N} f_r \cos 2\pi\left(\frac{hx_r}{a}+\frac{ky_r}{b}+\frac{lz_r}{c}\right)$$

$$B = \sum_{r=1}^{N} f_r \sin 2\pi\left(\frac{hx_r}{a}+\frac{ky_r}{b}+\frac{lz_r}{c}\right)$$

$$\text{and} \qquad \tan\alpha_{h,k,l} = B/A$$

Here f_r is an atomic scattering factor, which is known from wave mechanical considerations, and (x_r,y_r,z_r) are the co-ordinates of the centre of the rth atom of the N which make up the structure. Thus, if approximate co-ordinates are known, an approximate value of $\alpha_{h,k,l}$ can be calculated and it can be shown that the substitution of this in (1) with the experimentally determined $|F_o(h,k,l)|$, and the subsequent location of maxima in electron density, lead to an improved set of (x_r,y_r,z_r). Repetitions of the process lead to convergence to very accurate atomic co-ordinates.

The whole process may be exhibited in cyclic form : (1) rough approximations of (x_r,y_r,z_r) ; (2) compute $\alpha_{h,k,l}$; (3) locate maxima in $\rho(xyz)$ using $|F_o(h,k,l)|$ and $\alpha_{h,k,l}$; (4) compute $|F_c(h,k,l)|$ using maxima found in (3) ; (5) calculate discriminating function ; (6*a*) if unacceptable repeat from (1) using the co-ordinates found in (3), (*b*) if acceptable print out co-ordinates and stop.

The only step which requires explanation is (5). One discriminating function is :

$$R = \sum_{h,k,l} \| F_o(h,k,l)| - |F_c(h,k,l)\| / \Sigma |F_o(h,k,l)|$$

which can be shown to decrease to a value less than 0·20 as the process converges to the solution required.

The operations described are all ideally suited to a computing machine and it is only necessary to mention that the time for processing a complete structure of moderate complexity (twenty distinct atoms, say) has been reduced from three years to as many weeks. In fact the actual computing time is now far shorter than the time required to obtain the experimental results and to do the preliminary and incidental 'thinking'. The latter is important since, despite popular utterances to the contrary, the computer is not yet within sight of replacing the scientist.

Finally, a brief mention of the non-numerical applications of computing machines. These include the playing of games, the composition of music and poetry, and the translation of languages. At least one musical 'composition' by a computer which I have heard appeared to me preferable to the effusions of certain distinguished modern composers, but the poems leave much to be desired. Language translation has now reached the state of practicability, and awaits only the funds to construct *ad hoc* machines for it to be useful[13].

The playing of games on computing machines is interesting both for amusement and for the light which it throws on the problem of intelligent thought.

Nim and 'noughts and crosses'[14] can, of course, be played perfectly by a computer since they fall into the class of determined games; a satisfactory game of draughts appears now to be possible[15] but chess is still beyond the capacity of existing machines. Intelligent thought by machines poses a question which is largely one of definition. During a conversation between myself and R. W. Hamming the following was suggested: if a machine is set to play a simple game such as 'noughts and crosses' against a human being, it is exhibiting at least some of the characteristics of intelligence if, knowing only the size of the square and its own 'move' (that is to say, *O* or *X*), it can deduce from the results of several games the required configuration for a win, and play accordingly. Deduction by exhaustion, or playing all possible games, is not considered to be a valid solution. No programme of this type has yet been written.

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IMPERIAL CHEMICAL INDUSTRIES, LTD.: PHARMACEUTICALS DIVISION

NEW RESEARCH LABORATORIES

By Dr. J. YULE BOGUE

THE new pharmaceutical research laboratories of Imperial Chemical Industries, Ltd., at Alderley Park, Macclesfield, Cheshire, were formally opened by Lord Waverley on October 1, just twenty-one years after the Company's first entry into the pharmaceutical field. These laboratories represent the culmination of an expanding endeavour which, from the beginning, placed great faith in the possibilities of inventive research in the fields of applied organic chemistry and experimental biology. The discovery through the past years of such important drugs as 'Sulphamezathine', 'Paludrine', 'Antryeide', 'Mysoline' and, more recently, 'Fluothane' and 'Helmox', justifies the early faith in the potentialities of research of this nature. The development has meant the gradual addition of different scientific disciplines to create the balanced research organization which now exists in its new quarters.

Alderley Park extends to some 350 acres, of which the laboratories occupy only a small part, leaving plenty of land for farm animals—an essential feature in the study of diseases which afflict domestic animals.

The landscape is attractive, with the woodlands which surround the park ensuring privacy. The main block of buildings enjoys a superb view over Radnor Mere, where many wild birds find sanctuary.

A novel feature, which has influenced the design of the experimental animal houses, is a rat- and mouse-breeding unit designed to produce specific pathogen-free animals. For many years, research both in Great Britain and elsewhere has been severely hampered by the common infections inevitably found in commercial stocks of laboratory animals. The animals, delivered by Cæsarian section with sterile precautions and artificially reared to weaning under strictly aseptic conditions, are free from their natural infections. These animals can be maintained in the disease-free state and produce disease-free offspring provided they are protected from contact with outside sources of infection. Everything which enters or leaves the breeding unit has to pass through a routine of decontamination or sterilization. Staff pass from changing and decontamination rooms, through a disinfectant trough and air locks fitted with ultra-violet and electrical insecticidal dispensers. The entry of equipment and the issue of animals and processed feeding stuffs takes place through double-entry autoclaves, designed so as to prevent both ends being opened at the same time, thereby maintaining an aseptic 'lock' between the unit and the outside.

The breeding rooms have no windows and no natural ventilation. The treated air is changed ten times an hour without recirculation. The scale of operation, 500,000 animals a year, presented several novel problems. The manhandling of 45 tons of drinking water and bottles a week was avoided by an automatic watering system. Flushing of the racks is also automatic.

In the experimental animal houses the natural pathogens of mice and rats are kept out by means of vermin-proof barriers at strategic points. Each animal cell opens on to a verandah screened to keep out birds. The verandah access allows air dilution to reduce the risk of cross-infection to a minimum. Separate ventilation and independent temperature control of each animal cell are other features.

In the infectious diseases animal house, staff and attendants must pass through clothes-changing routines in the decontamination locks. Colour coding also plays a part. On the virus floor, cell doors painted in various colours indicate animals infected with separate diseases. Inside, all movable equipment is given the same colour, while operators wear coloured overalls. The colours must never be mixed. In diseases dangerous to man, the principle adopted

is that of containment. The infected animals are housed in ventilated cupboards located on each side of a ventilated manipulation hood fitted with glove ports.

The non-infectious animal house serves physiology, pharmacology, parasitology and pathology. In addition to housing the pathogen-free rats and mice, the standard cells have been adapted to serve as insectaria, snail room, chick rooms and so on.

The biological laboratories are arranged in suites of three rooms, of which the two outer, one a mirror image of the other, flank a central area devoted to a study space and utility area. Fexibility is the keyword of their design. The laboratory furniture, instead of being fixed, can be moved to suit the individual needs of the worker. Welded steel table frames carry stainless steel, hardwood or plastic tops. Flexibility is maintained by bringing the services into the laboratory in repetitive units which carry electricity, gas, vacuum, air, water, drainage and, where required, steam. The outlets are grouped in units at 5-ft. intervals on each lateral wall. In addition, there are two floor outlets in the centre line of the laboratory which are readily tapped through optionally removable service pedestals. Cylinder gas outlets are provided on one wall, and the cylinders are housed in cupboards in the corridor to eliminate trundling them into the laboratories.

The central utility area may house sterile cubicles with bacteriologically filtered air, centrifuge and ventilated hoods, smoking and varnishing units, electrostatically screened rooms, dark rooms, etc. The window side of the central unit provides office or study facilities for both laboratories. The windows of the biological laboratories are double. The outer window can be opened for cleaning while the inner portion is a single sheet of plate glass permanently fixed. The space between is provided with a heating coil and a remote-controlled venetian blind.

Each floor contains a series of constant-temperature rooms providing temperatures ranging from — 70° C. to blood heat.

The chemical laboratories set fewer problems than the biological ones. The basic design is similar to that of the standard synthetic laboratories in the Dyestuffs Division, namely, two laboratories each accommodating four chemists, with office space between. In addition, there is provision for a number of special services and techniques. Physical chemistry and biochemistry, with their high degree of instrumentation, both required special accommodation. There are also specially designed laboratories for micro-analytical work, radiochemical investigations and the handling of highly toxic chemicals or gases. A large-scale laboratory is available for making large batches of intermediates or for the preparation of promising compounds for clinical trial. The area is flame-proof and it is here that the preliminary work on sealing-up can be carried out.

Centrally placed among the laboratory blocks are the wash-up, media kitchen and stores. The unit receives dirty and contaminated glassware for sterilization, washing, storage and re-issue. The lay-out is entirely subordinated to the flow of materials handled. Every effort has been made to reduce drudgery to a minimum through mechanical aids.

The total graduate staff accommodated in the new laboratories is approximately a hundred, of whom more than half are chemists (organic, physical, pharmaceutical and biological). The other scientific disciplines include bacteriology, virology, mycology, protozoology and helminthology. There are also units for pharmacology, physiology and pathology which cover the work on parasitic diseases and infections, the diseases of organic dysfunction and the pharmaceutical aspects of surgery such as anæsthetics. In addition to the graduate staff there is a staff of assistants and technicians and a general labour force. The overall total of employees on the site is about four hundred and fifty.

The entire work of the laboratories is concerned with the invention and discovery of new drugs and preparations for use in human and animal medicine. The broad scope of the research is indicated by the different scientific disciplines mentioned above. Administratively, the staff is divided into two groups, chemical and biological, each of which is in turn divided into a number of sections with defined responsibilities in a particular field. As a matter of practical day-to-day working there is a natural and non-formal division into flexible teams of scientists who are all collaborating on a common problem. This may be illustrated, by way of example, by the pattern of research on a particular bacterial disease. The natural team combination will emerge from: (1) Members of the chemical group whose duty it is to synthesize new compounds for evaluation. (2) Their opposite numbers in the biological group who are charged with the task of reproducing the disease in an experimental animal and providing an accurate assay procedure for the new chemicals which come along. The routine assay is, of course, only as good as the research behind it. (3) Biochemists who must, by studies of the mode of action, generate ideas upon which chemists engaged in synthesis can build. Later, as active drugs begin to emerge, pharmacology and pathology come into the picture, and also the pharmaceutical chemists who must present the potential new drugs in a form which is likely to be acceptable to the practising doctor or veterinarian.

The particular targets of research are generally decided by a combination of economic and technical factors. An industrial research laboratory must pay its way, and the products of successful researches must carry the burden of paying for the effort which does not produce its own monetary return. Research targets vary in their degree of feasibility or in the time which may be expected to elapse before useful results accrue. The work in progress at Alderley Park, therefore, has both long-term and short-term objectives. In the long-term category are studies on the chemotherapy of cancer and viruses. No quick answer can be expected in these fields which are closely related, as both involve the study of the intimate processes of cell division and the multiplication *in vivo* of macromolecular species. Knowledge gained in this kind of work is of value not only in a direct sense, but also for its bearing on the biochemistry of micro-organisms generally. Some of the research projects in chemotherapy may become progressively more difficult as knowledge advances. This apparent paradox arises because the discovery of a drug for the treatment of a particular disease automatically alters the objective. The requirement now is for a drug with improved properties, generally fairly precisely defined. For example, although it is not difficult to synthesize new chemical compounds with antimalarial activity, it is by no means easy to make one which is better than such drugs as 'Paludrine' or 'Chloroquin'. There are already many effective antibacterial drugs, and the problem now is

not so much to find a new antibacterial, as to find one which has specific properties overcoming the particular disadvantages or limitations of those which are already available to the doctor. It is not difficult to synthesize anæsthetics, but the recent invention of 'Fluothane' was the result of a deliberate search for a volatile anæsthetic having in particular the property of non-inflammability.

The projects under study at Alderley Park are divided broadly into infectious or parasitic and non-infectious diseases. The former includes diseases caused by viruses, bacteria, fungi, protozoa and metazoa. The non-infectious diseases include those of the nervous system (such as epilepsy), hypertension rheumatism and allergic phenomena (for example, hay-fever and asthma). This broad coverage, supported by first-class laboratory facilities and an enthusiastic staff, should pave the way for continuing advances in the chemotherapeutic treatment of disease.

THE ACCIDENT AT WINDSCALE

THE accident at the United Kingdom Atomic Energy Authority's Windscale No. 1 Pile on October 10 has rightly been taken very seriously by both the Government and the Authority. A Committee of Inquiry was set up by the Authority to investigate the cause of the accident and the measures taken to deal with it and its consequences. The White Paper dealing with the accident which has now been published* contains a memorandum by the Prime Minister together with six annexes. Instead of the original report on the cause of the accident which, in the national interest, is not being published, the first annex comprises a less technical and more qualitative account of the sequence of events.

One feature of a graphite-moderated reactor is that a considerable amount of energy is stored in the graphite due to atomic displacement caused by neutron bombardment. This is known as Wigner energy, and the phenomenon had been observed before the Windscale reactors were built. The energy can be 'released' by raising the temperature of the graphite, or it may release itself spontaneously. In either case, it is transformed into thermal energy and heats the graphite. The White Paper implies that this 'Wigner release' phenomenon was unknown at the time of construction of the Windscale reactors. A spontaneous release occurred in No. 1 Pile in 1952, without harmful effects, and since that time eight controlled releases have been carried out in the pile. To achieve the release, a small amount of nuclear heat is applied, with greatly reduced flow of coolant so as to maintain the graphite at a constant temperature but higher than normal. The operation demands careful control of the nuclear heating-level, based upon observations of the temperatures within the pile.

The Committee of Inquiry was satisfied that the thermocouples in the pile, while adequate for normal operation, were neither sufficient nor correctly placed for the Wigner release operation, nor was the power-level meter accurate enough at the lower powers being used. It appears, moreover, that insufficient instructions had been given to the operators to enable them to deal reliably with the conditions arising. In previous Wigner releases, two nuclear heating operations had proved necessary to obtain complete release. In the opinion of the Committee, the second heating was, on this occasion, applied before it was necessary, and too much of it was applied too quickly. Some cartridges were ruptured, most probably cartridges containing fuel. The further rise in temperature as Wigner energy was released caused the exposed uranium, and eventually the graphite, to burn. It appears that some two days elapsed between the occurrence of the rupture and its detection, during which time the fire spread. After several unsuccessful attempts to extinguish it by careful air control, water was successfully used.

The Committee found that the steps taken to deal with the accident, once it had been discovered, were prompt and efficient, and displayed great devotion to duty on the part of all concerned.

Annex 2 contains the report of the Committee on the measures taken to deal with the consequences of the accident, and concerns actions taken to protect the workers and the public. A report by an independent committee to the Medical Research Council is included as Annex 3, and these two annexes should be considered together.

When an out-of-door air sample showed an activity of upwards of ten times the normal level, precautionary measures were taken to protect the workers on the plant.

These included frequent sampling over the site, orders to the workers to remain indoors and to wear face masks, and an inspection of canteen food. Examination of the total-body radiation and thyroid absorption showed that some workers received doses greater than the recognized limit for continuous operation, and they will, therefore, be removed from radioactive work for a period. Strontium and cæsium absorption appear to have been insignificant. These conclusions are endorsed by the Medical Research Council Committee.

Dealing with the measures taken to protect the public, the Medical Research Council Committee agreed that the health physics manager correctly assessed that the main problem might arise from ingestion of contaminated food. It directs attention to the delay between recognition of a possible radioactive hazard to the surrounding countryside, and the institution of extensive and rapid milk sampling. It appears that thirty-four hours elapsed between the recognition of this possible hazard and the receipt of the first milk analyses, and some seven hours between the receipt of the first seriously contaminated milk and the decision to prevent deliveries. It is not stated at what stage a milk analysis was ordered, nor how long such an operation takes.

It appears that it had not been anticipated that iodine vapour would escape from the filter in preference to particulate fission products, and that information was not available to deal with this situation.

* Atomic Energy Office. Accident at Windscale No. 1 Pile on October 10, 1957. (Cmnd. 302.) Pp. 26. (London: H.M. Stationery Office, 1957.) 1s. 3d. net.

The Medical Research Council Committee concludes that, despite these shortcomings, the protection measures were essentially right and, once brought into play, were applied decisively, and were adequate. It is convinced that it is in the highest degree unlikely that any harm has been done to anybody.

The chairman of the Atomic Energy Authority has accepted full responsibility for the accident, and at his request further inquiries are in hand to undertake a technical evaluation of information arising from the accident, and to review organization problems concerned with reactor operation.

A short, but convincing, note by the Authority gives several reasons why this accident could not happen with the Calder Hall or the new Electricity Authority reactors.

Much experience and information have been gained from the accident, without, so far as can be judged, any ill effects on humanity. We are fortunate in that the cause and history of the accident have almost certainly been traced, and we can be especially thankful for those much-criticized excrescences at the top of the ventilation stacks, the radioactivity filters.

W. Murgatroyd

OBITUARIES

Dr. Gerty T. Cori

Dr. Gerty T. Cori, who died at St. Louis, Mo., on October 26, was a most distinguished biochemist. In 1947, Prof. Carl F. Cori, her husband, and she shared with Prof. B. A. Houssay, of Argentina, the Nobel Prize for Medicine and Physiology.

Gerty Cori was born in Prague, Czechoslovakia, graduating in medicine from the German University in that city in 1920. In the year she graduated she married a fellow medical student, Carl Cori, by whom she later had one son. In 1922, Carl and Gerty Cori moved to the United States, becoming American citizens in 1928. Until 1931 they worked at the State Institute for the Study of Malignant Diseases at Buffalo, N.Y., and in 1931 they moved to St. Louis, where ultimately they both held professorships of biochemistry in the School of Medicine of Washington University.

Their principal researches have been in the field of carbohydrate metabolism, with particular reference to the mechanism of breakdown and building up of glycogen and the influence of hormones on the processes. In their early researches at Buffalo they discovered the 'Cori cycle', whereby lactic acid produced in mammalian muscle is converted to liver glycogen and thence can go via blood sugar to muscle glycogen and so back again to lactic acid. Their characterization of phosphorylase and their identification of the then unknown glucose-1-phosphate as the product of the action of the enzyme on glycogen under suitable conditions were of outstanding importance in the elucidation of pathways whereby glycogen is broken down and built up in muscle and liver. This discovery led to the first *in vitro* production of glycogen, which took place in their laboratory. Before this could be done, they characterized a branching enzyme (amylo-1 : 4-1 : 6-transglucosidase) in muscle which converts some 1 : 4 links of the amylose formed from glucose-1-phosphate, under the influence of phosphorylase, into 1 : 6 linkages, and thus produces a branched polysaccharide—in this instance glycogen—from a straight-chain one, namely amylose. In conjunction with her pupils during the past few years, Gerty Cori has, despite a rapidly growing illness, developed an enzymic method for assessing the molecular architecture of glycogen. Using such methods, she has differentiated several types of glycogen-storage disease according to differences in the enzymes and abnormalities of the structure of the stored glycogen.

The researches of Gerty Cori and her colleagues concerning the influence of insulin on the enzyme hexokinase are still a matter for discussion, but undoubtedly they have given rise to much fruitful investigation regarding the fundamental action of insulin all over the world.

Gerty Cori was a charming hostess as well as an outstanding scientist, being a woman of wide general culture and interests. A brave woman, outstanding as a scientist among scientists, she has left a permanent record of herself in numerous laboratories, not only in publications but also in the wide influence she exerted on research in the difficult field of carbohydrate metabolism

F. G. Young

Prof. J. A. S. Ritson, O.B.E.

John Anthony Sydney Ritson, emeritus professor of mining in the University of London, died on October 16 at the age of seventy. He was born at Pelton, Co. Durham, on August 18, 1887, and was educated at Uppingham and the University of Durham.

As a Rugby player he was capped several times for England between 1910 and 1913 and never in later life lost his love for the game which so appealed to the 'Geordie' side of his temperament. In the First World War his crisp and firm appraisal of men and situations won him the command of the 12th Royal Scots, a regiment he led with dash and distinction from 1916 until 1919. His battle honours included the D.S.O. and bar, the M.C. and four 'mentions'. After a post-war period as H.M. Inspector of Mines, during which he served successively in Scotland, Yorkshire and South Wales, he was appointed to the chair of mining in the University of Leeds in 1923.

In 1935 he was made O.B.E., and in the following year took over the chair of mining at the Royal School of Mines (one of the three associated Colleges which form the Imperial College of Science and Technology, London). Here his love of manly sports, his directness of approach and the whole-hearted way in which he embraced the cause of his students won him a host of friends. His long memory for names and faces was a valuable asset in this connexion, since metal miners go out from the Royal School of Mines all over the world and international social contacts are important. In addition to his academic activities, he did valuable work on O.E.E.C., where he helped to generate post-war interests in the development and treatment of low-grade ore deposits. Part of the fruits of his work, in which he took an important role, was the institution of the first degree course in the world in mineral dressing, at the Imperial College.

He took a serious operation in his stride in 1950. After he retired in 1952 he continued with a busy consulting practice in addition to his work with the Institution of Mining and Metallurgy and the Institution of Mining Engineers, in each of which he had been president. During the Second World War he did much work for the Ministry of Mines, but was never too busy to find time to see an old student. Other bodies which he served included the Geological Survey of Great Britain, the Coal Commission and the Natural Resources Commission. He was, until his death, the Crown mineral agent.

In addition, his consulting practice took him to many foreign countries and Dominions. We who worked under him learned to value his small human weaknesses not less than his qualities of leadership. He leaves a widow and two sons.

E. J. PRYOR

NEWS and VIEWS

Royal Medals of the Royal Society

H.M. THE QUEEN has been graciously pleased to approve recommendations made by the Council of the Royal Society for the award of the two Royal Medals for the current year as follows: Prof. W. V. D. Hodge, Lowndean professor of astronomy and geometry in the University of Cambridge, for his distinguished work on algebraic geometry; Prof. F. G. Gregory, professor of plant physiology at the Imperial College of Science and Technology, London, for his distinguished studies in plant physiology.

The New Scientist

THE first anniversary issue of *The New Scientist* appeared on November 21. As H.R.H. Prince Philip says in a congratulatory letter, its birth could not have been more opportune. The accident at the Windscale factory, nuclear power and space travel have further stimulated the layman's interest in the activities and achievements of scientists. *The New Scientist*, as especially shown in its articles on the artificial Earth satellites, is admirably suited to satisfy their curiosity. It is one of the few realistic attempts to bridge the gulf between the scientists and non-scientists. Besides Prince Philip's letter, this issue, which marks the beginning of the journal's second year (vol. 3, No. 53), includes articles on "The Present Golden Age", by Sir Charles Darwin; "X-Ray Analysis", by Sir Lawrence Bragg; "Submarine Oil Tankers", by Nigel Calder; "Progress of Quick Freezing", by Dr. J. Hawthorn; and "Ragworms and Caviar", by Dr. R. P. Dales; there is also a Christmas book section. We offer *The New Scientist* our congratulations and best wishes, and feel sure that there will be many more anniversary issues.

500,000th Leitz Microscope: Dr. Paul A. Weiss

PROF. PAUL A. WEISS, head of the laboratory of developmental biology of the Rockefeller Institute, received the 500,000th microscope made by the firm of Ernst Leitz at a brief ceremony in his laboratory. The presentation of the microscope to Dr. Weiss is in the tradition of special recognition given by the Leitz organization to famous scientists for their fundamental contributions to the knowledge of living structures and their development and pathology. He is the first American to be so honoured. Robert Koch, discoverer of the tubercle bacillus, received the 100,000th Leitz microscope in 1907; Paul Ehrlich, pioneer in chemotherapy, the 150,00th in 1912; Martin Heidenhain, the histologist, the 200,000th in 1921; Ludwig Aschoff, the pathologist, the 300,000th in 1930; and Gerhard Domagk, Nobel prizeman for his work for chemotherapy, the 400,000th in 1949. Dr. Weiss, whose biological researches have covered a wide field, is known for his work on the analysis of the development and growth of living structures.

Royal Aircraft Establishment Appointments: Mr. R. W. Pye

MR. R. W. PYE has been promoted deputy chief scientific officer as head of the Trials Department of the Royal Aircraft Establishment. Mr. Pye graduated in mathematics at Cambridge in 1933 and joined the Royal Aircraft Establishment in 1936, when he worked on problems of airborne gunnery and the aerodynamics of winged torpedoes. During the War he was responsible in the London Headquarters for a range of armament research. At the beginning of 1947 he went to Australia in the team led by Lieut.-General Evetts to initiate the setting-up of the rocket range at Woomera. For the past eighteen months of his stay in Australia he was acting chief superintendent of the Long Range Weapons Establishment (now Weapons Research Establishment) at Salisbury and made important contributions to the planning and installation of the range facilities. Since his return to England in mid-1950, Mr. Pye has been intimately concerned with the extension of the guided weapon ranges in the United Kingdom and the introduction of new and advanced trials instrumentation techniques.

Mr. P. A. Hufton

MR. P. A. HUFTON has been appointed to the new post of head of the Bedford Divisions, Aerodynamics Department. In this post, which carries the rank of deputy chief scientific officer, he will take charge of the aerodynamic flight testing and wind tunnel testing at the Royal Aircraft Establishment, Bedford. Mr. Hufton took his M.Sc. at the University of Manchester in 1934 and then joined the staff of the Royal Aircraft Establishment where he worked throughout the period 1934–46 on various aerodynamic research problems, specializing in research on aircraft in flight. In 1946 he moved to the A. & A.E.E., Boscombe Down, as superintendent of performance and in 1953 returned to the Royal Aircraft Establishment to take charge of the Supersonic Division, Aerodynamics Department, a post which he has held until his present appointment. He rapidly became expert in the expanding field of hypersonic aerodynamics, and under his leadership a strong research team was built up. During this period he was promoted to deputy chief scientific officer and acted as head of the Aerodynamics Department throughout 1956 while Mr. L. F. Nicholson was at the Imperial Defence College.

Dr. D. Küchemann

Dr. Dietrich Küchemann has been promoted to the rank of deputy chief scientific officer and appointed head of the Supersonics Division of the Aerodynamics Department at the Royal Aircraft Establishment. Dr. Küchemann studied under Prandtl at Göttingen where he obtained his doctor's degree in 1936. Remaining in Göttingen for the next ten years he worked at the Aerodynamische Versuchsanstalt under Prof. Betz. During this period he became an acknowledged expert on propulsion aerodynamics and much of his understanding and new thought on these problems was crystallized in the book "Aerodynamics of Propulsion" published in 1953, in which he collaborated with Dr. Weber. In 1946 he came to England and has since worked in the Aerodynamics Department of the Royal Aircraft Establishment where his personal researches were acknowledged in 1954 by his appointment as a senior principal scientific officer on individual merit. While at the Royal Aircraft Establishment Dr. Küchemann has made major contributions to the methods of design of swept wings and the junction of such wings with bodies and nacelles, particularly at transonic speeds. More recently he has worked on problems of wing stalling and flow separations and has been mainly responsible for the important work leading towards an understanding of the vortex type flow around slender wings.

Linnean Society of London : Centenary Celebrations, 1958

The Linnean Society of London is arranging to celebrate in 1958 the 200th anniversary of the publication of the tenth edition of the "Systema Naturae" of Linnaeus, and the centenary of the joint communication made to the Society by Darwin and Wallace on evolution by natural selection. A memorial tablet will be unveiled on July 1 in the rooms of the Society commemorating the reading of the Darwin–Wallace communication. This will be followed by a dinner of the Society. A special meeting of the Society will be held in the Memorial Hall of the Royal Geographical Society, Kensington Gore, on July 15, at which two papers will be read on the work of Linnaeus by Dr. A. Tindell Hopwood and Dr. A. J. Cain. These will be followed by a presentation of Darwin–Wallace Silver Medals to a number of British and foreign zoologists and botanists. A joint conversazione with the Royal Society and the Geological Society will be held at Burlington House on the evening of July 15, at which Darwiniana and Wallaciana will be exhibited. A Darwin–Wallace memorial number of the *Journals of Botany* and *Zoology* is to be published containing the text of Dr. Julian Huxley's Darwin–Wallace Lecture which will be delivered in the Royal Albert Hall at the opening session of the International Congress of Zoology on July 16, together with some fifteen original contributions from distinguished botanists and zoologists working in the field of evolution. Bronze replicas of the Silver Darwin–Wallace Medals (in case) will also be available for purchase.

The Convergatron

At a meeting of the American Nuclear Society, on October 29, Dr. Lyle B. Borst, chairman of the Department of Physics, College of Engineering, New York University, described a new design for nuclear power plants. Dr. Borst envisaged a subcritical reactor controlled by a small neutron source and amplified by a 'convergatron'. This is a neutron amplifier which magnifies the flow of neutrons in a manner analogous to that of the thermionic valve and the transistor. A series of convergatrons would amplify neutrons from a weak source to a large power reactor, and yet the power plant itself would shut off upon the removal of the source. Because all parts are subcritical, there is no danger of losing control of the chain reaction.

The convergatron consists of three sections—one containing the pure neutron moderator such as plain water or graphite, one containing unenriched uranium-238, and a thermal neutron barrier such as cadmium. Fast neutrons from the fission of uranium in the fuel zone penetrate the cadmium barrier. They are slowed by the moderator to become thermal neutrons that activate the next fuel zone. The fast neutrons starting in the reverse direction are slowed by the moderator until they can no longer penetrate the cadmium. Each fuel zone receives neutrons from the preceding stage. Therefore each succeeding stage can operate at a higher power while still depending upon the preceding stage for its excitation. With several stages, the convergatron, acting as a power source through heat transfer, should be able to generate enough power to make the system practicable in many areas of the world.

Nuclear Power Stations and Public Health Hazards

Several questions about nuclear power stations were dealt with in the House of Commons on November 11 by Mr. D. L. M. Renton, who repeated that if public confidence were shaken at all by what happened at Windscale (see this issue of *Nature*, p. 1093), so far as Calder Hall and the Electricity Authority's nuclear power stations are concerned, confidence should be completely restored by the White Paper and the Prime Minister's statement. As regards the suggestion of an independent inspectorate, the Atomic Energy Authority has prepared safety regulations for Broadwell power station and a permanent safety staff is already drawing up a formal safety code of procedure for both the design and the operation of nuclear reactors. The suggestion of a public monitoring system would receive consideration. A public inquiry will be held into the proposal to build a nuclear power station within the Snowdonia National Park ; but in reply to the suggestion of a full inquiry into the whole question of the siting of nuclear power stations instead of dealing with them individually, Mr. Renton thought that individual inquiries as required were the best way of dealing with the matter.

Afterwards, on November 12, replying to a question whether he would consider setting up a special department within the Factory Inspectorate to select and train inspectors for the nuclear power stations, the Parliamentary Secretary to the Minister of Labour, Mr. L. R. Carr, said that this is not considered necessary. Four inspectors in the Chemical and Engineering Branch and twenty-one in the districts have already been trained, and fifty more are to be trained under a programme covering protection against radiation hazards in industry generally, including nuclear power stations. Two inspectors in the Chemical and Engineering Branch have also received training in the design, maintenance and operation of reactors.

Progress in the Commercial Use of Atomic Energy

The Paymaster-General, Mr. R. Maudling, replying to a question on November 11 in the House of

Commons about progress in the development of a package nuclear reactor for export purposes, said that recent studies have suggested that the Calder Hall type of reactor should be capable of modification to produce electricity at a competitive price from small stations of about 20–30 megawatts capacity. Other reactor systems that might be suitable for generating electricity in smaller power stations are being investigated, and two British firms have marketing rights for small power reactors of American design. British manufacturers have received a number of inquiries and are actively exploring possible markets for the types they can offer. Research is proceeding into many types of reactors; Mr. Maudling added that he understood that small reactors for civil use are not yet operating in the United States and that there is no proof of their reliability or economy.

Further questioned as to controlled thermonuclear fission, Mr. Maudling said that the experimental apparatus at Harwell known as ZETA is now operating, and discharges through heavy hydrogen gas have yielded very high temperatures. Experiments are proceeding to identify the source of the accompanying neutron emission, which probably arises from thermonuclear reactions but may be due to other complex nuclear processes. Many major problems remain to be solved before the practical application of thermonuclear reactions could be considered, and although research and development in this field are being given the highest priority, the work must be expected to remain in the research stage for some years.

Responsibility for Atomic Energy Developments

In reply to a question in the House of Commons on November 12 as to whether, in view of the fact that responsibility for nuclear energy matters involves much detailed study of highly technical problems, he would consider transferring that responsibility from himself to a senior Minister in the House of Commons, the Prime Minister said that he considered that the existing arrangement is the most suitable at the present time. There are disadvantages, but when the various uses of nuclear energy are so much in the field that the Prime Minister of the day is bound to have them under his control, there are advantages and the system works fairly well; in the detailed work, he said, he is being greatly helped by the Paymaster-General.

Instrumentation of British 'Skylark' Rockets

A 'Skylark' high-altitude research rocket, fired in darkness at the Woomera rocket range on November 13, reached a height of 83 miles. It was the fourth of six proving rockets scheduled to be fired before the beginning of a joint programme of upper atmosphere research by the Royal Society and the Royal Aircraft Establishment. The first three firings having shown the performance of the rocket vehicle and its 'Raven' solid-propellant motor to be satisfactory, attention has been turned to trials of rocket-borne and ground equipment. 'Skylark No. 4', in addition to routine instrumentation, such as timing gear, telemetry sender, power supplies and Doppler transponder and microwave beacon used for tracking purposes to give velocity and position, carried equipment for four separate high-altitude measurements. First, eighteen grenades were ejected from the rocket at 3-sec. intervals at altitudes above 100,000 ft. On the ground microphones recorded the time of arrival of the sound waves, ballistic cameras recorded the positions in space of the flashes and a detector recorded the instant of each flash. The experiment, which is being made by University College, London, aims at measuring atmospheric temperatures and high-altitude wind velocities. Secondly, fourteen cartridges of 'window' (strips of fine metal foil) were released explosively in two clouds at different heights above 100,000 ft. and followed by tracking radars. The experiment, devised by the Imperial College of Science and Technology, London, is designed to measure winds at altitudes up to 50 miles. Thirdly, a section of the rocket nose was insulated from the remainder of the body to make a condenser of fixed capacity forming part of a 5 Mc./s. oscillatory circuit for measuring ionospheric electron densities, the results being telemetered to the ground. Devised by the University of Birmingham, this ingenious device will be more effective in later rockets which will penetrate farther into the ionosphere. Finally, three Pirani pressure gauges were carried in the rocket cone, one measuring ram pressure in the very tip of the nose, the other two measuring cone-wall pressures. These measurements, being made by the Royal Aircraft Establishment, enable the undisturbed ambient pressure at various altitudes to be determined.

British Computer Society: Glasgow Branch

At a meeting, held on November 11 in the Chartered Accountants Hall, Glasgow, to inaugurate the Glasgow Branch of the British Computer Society, a committee was appointed, initially for the period until April 1958. Mr. K. D. Henderson was elected convener and honorary secretary and the following were elected members of the Committee: Dr. D. C. Gilles, Mr. W. B. Mackay, Prof. D. C. Pack, Mr. T. B. Simpson and Mr. J. J. B. Young. The committee is arranging a series of lectures by people experienced in the application of electronic computers, the first of which will be given in December. In due course, study groups will be formed to consider various aspects of the application of computers to commercial, engineering and scientific work. Inquiries can be addressed to Mr. K. D. Henderson, 89 Wellington Street, Glasgow, C.2.

Information and Control

Information theory has grown so rapidly and has found applications in so many fields that the new journal, *Information and Control* (New York: Academic Press), can play a valuable part in centralizing research results. The editors are L. Brillouin (New York), C. Cherry (London) and P. Elias (Cambridge, Mass.), and there is a strong international supporting editorial board. The journal will publish work on the theories of communication, computers and automatic control, but it will also accept papers offering experimental evidence or theoretical results bearing on information theory, from related fields. In the first number, Brillouin's editorial is essentially a comment on Born's form of Occam's razor: "concepts which refer to distinctions beyond possible experience have no physical meaning and ought to be eliminated". Of the eight other items, special reference may perhaps be made to the paper by G. A. Miller and E. A. Friedman, in which, following a suggestion due to Shannon, the authors discuss various experiments in reconstructing mutilated texts.

Journal of Applied Bacteriology

The *Journal of Applied Bacteriology* is normally published bi-annually, issues appearing in June and December. In 1957 three numbers will be published, the third appearing in December. This extra number of the *Journal* will contain the papers read at a special symposium of the Society for Applied Bacteriology held in July last. The subject of the symposium was "Bacterial Spores". Orders for the special issue (35*s*.) and new orders for the *Journal* (35*s*. per issue) should be sent to Mr. A. H. Walters, Honorary Publications Manager, Society for Applied Bacteriology, Milton-Deosan Research Laboratory, 64 Wimpole Street, London, W.1.

Grant to the Macaulay Institute for Soil Research

The Rockefeller Foundation has made a grant of up to 9,500 dollars to the Macaulay Institute for Soil Research for the development of spectrochemical methods of analysis. This grant will be used for purchasing a British-made 11-channel direct reading attachment to a medium quartz spectrograph. This equipment, which enables analyses of chosen elements to be carried out automatically in an electric discharge, will allow the Department of Spectrochemistry to develop its investigations of the role of trace elements in soil–plant relationships and other biological problems.

Oversea Service Division, Colonial Office

The following appointments have recently been made in the Oversea Service Division, Colonial Office: P. W. A. Davies (agricultural officer, Kenya), agricultural officer, Basutoland; G. Gamble (provincial agricultural officer, Kenya), assistant director of agriculture (Field), Kenya; E. C. M. Green (agricultural officer, Kenya), provincial agricultural officer, Kenya; R. J. Spooner (agricultural officer, Kenya), provincial agricultural officer, Kenya; R. J. Dewar (deputy conservator of forests, Nyasaland), deputy chief conservator of forests, Nyasaland; R. G. M. Willan (conservator of forests, Nyasaland), chief conservator of forests, Nyasaland; R. M. C. Williams (scientific officer, East Africa High Commission), senior scientific officer, East Africa High Commission; G. Froyd (veterinary officer, Kenya), veterinary research officer, Kenya; M. I. Ashrif, agronomist, Sierra Leone; T. M. Denoon, temporary livestock superintendent, Department of Veterinary Research, Federation of Nigeria; R. Hewson, agronomist, British Guiana; L. B. Palmer, agronomist, British Guiana; J. M. Taylor, development officer, pig industry, Jamaica; J. B. Robertson, fisheries officer, Tanganyika; C. W. Holloway, assistant conservator of forests, Kenya; M. G. Allderidge, assistant geologist, British Guiana; L. L. Fernandez, assistant geologist, British Guiana; P. Rix, geologist, Kenya; D. J. L. Casley, statistician, East Africa High Commission; R. G. Erskine, temporary veterinary research officer, Federation of Nigeria; T. M. Leach, chief veterinary officer, Northern Nigeria; B. J. Hills, metallurgist, Tanganyika; D. W. Parry, cartographer, Kenya.

Announcements

Dr. Gerhard Herzberg, director, Division of Pure Physics, National Research Council of Canada, has been elected an Honorary Fellow of the National Academy of Sciences, India.

Mr. Philip Sheridan Hopkins, professor of aviation and head of the Department of Aviation at Norwich University, Vermont, has been appointed director of the Smithsonian Institution's National Air Museum.

At a recent meeting of the Board of the British Nuclear Energy Conference, the Institute of Fuel was admitted to membership. The purpose of the British Nuclear Energy Conference is to co-ordinate the activities of the constituent members in the field of nuclear energy; meetings are held and a journal is to be published.

The Company of Glass Sellers offers scholarships in glass technology, tenable at the University of Sheffield. The scholarship examination consists of papers in chemistry, physics and mathematics. Entry forms (which must be returned by February 1) and further information can be obtained from The Registrar, University of Sheffield, Sheffield, 10.

The Nutritional Biochemicals Corporation, of Cleveland, Ohio, has issued a new catalogue of research 'biochemicals' (October 1957). There are a few new items, including decarboxylases for the natural forms of the amino-acids arginine, aspartic acid, histidine, lysine and tyrosine. Biochemists will note wistfully that 1 gm. of coenzyme A (75 per cent) still costs 600 dollars, though there are some price reductions.

Prof. C. E. H. Bawn will deliver the fourth lecture of the Plastics Institute for young people on "The Progress of Plastics" in the William Beveridge Memorial Hall, Senate House, University of London, W.C.1, at 2.30 p.m., on January 2, 1958. Admittance will be by ticket only, obtainable from the Secretary to Council, Plastics Institute, 6 Mandeville Place, London, W.1.

The annual meeting of the Science Masters' Association will be held in the University of Leeds during December 31–January 3. Further information can be obtained from the annual meeting secretary, W. H. Dowland, 93 Westbourne Road, West Hartlepool, Co. Durham.

The 124th meeting of the American Association for the Advancement of Science will be held in Indianapolis during December 26–30, with headquarters in the Claypool Hotel. In addition to the eighteen sections of the Association, some seventy affiliated and associated societies will also meet. Further information can be obtained from Sidney S. Negus, Medical College of Virginia, Richmond, Virginia.

A three-day meeting of the Society of Glass Technology is to be held at Elmfield, Northumberland Road, Sheffield 10, during November 26–28. The programme includes delivery of the presidential address on "Forty Years beside the Glass Industry" by Mr. C. E. Ramsden (on November 26) and a symposium on "Radioisotopes and Glass" (on November 27). Further details may be obtained from the Society of Glass Technology, Thornton, Hallam Gate Road, Sheffield 10.

Erratum. In *Nature* of August 10, p. 296, the legend to Fig. 1 of the communication on "Photoperiodicity and Wool Growth in Romney Rams and Wethers" by Dr. A. B. Wildman should read: "Weight of clean wool conditioned to 67° F., 65 per cent relative humidity from tattooed squares".

EDUCATION AND THE UNDER-DEVELOPED TERRITORIES

SIR SYDNEY CAINE'S paper, "Education for Development", read on September 9 before Section L (Education) at the British Association meeting in Dublin, was in the vein of Prof. P. M. S. Blackett's presidential address. Although, like Prof. Blackett, Sir Sydney was concerned largely with the under-developed countries, much of what he said about the part which education has to play in the business of development bore closely on economic or industrial development anywhere, whether in the developed or the under-developed countries. As Sir Sydney pointed out, the real difference between such countries lies in the magnitude of current incomes and current capital equipment. Broadly, the under-developed countries are the poorer countries of the world and the developed are the richer, and though there may be no precisely agreed definition as to the meaning of richer or poorer, there is rarely uncertainty as to the category to which particular countries belong.

If, further, we remember that at the bottom of the process of development is the creation of wealth, and that this in turn depends on the application to a country's basic national resources of human skills and labour, assisted by capital, in turn the product of human effort, it is understandable how largely education is the common factor and the common problem. Without human skill and labour, natural resources are indeed useless, and of capital Sir Sydney remarked again that it depends on human endeavour and human abstinence to bring it into existence. The spread of knowledge and skill is fundamental to the whole creation of wealth.

Sir Sydney passed briefly over the question of technical knowledge, without deprecating it, emphasizing that merely technical knowledge is by no means enough. It must be supported by advancing fundamental scientific knowledge, as well as by the habit of mind, apt to be overlooked in the West, which accepts and applies technology, combining theoretical knowledge from books and laboratory experiments with the readiness to engage in hard and dirty labour. Again, the technologist needs also the support of more general education in two senses. Besides the creation of more wealth, full and healthy social and economic development involves raising the level of social organization and economic capacity, and this can only follow as the level of education is raised. Secondly, economic developments do not occur in isolation; and the production of more wealth brings new problems of distribution and utilization, the solution of which requires men and women trained in economics and social science as well as in natural science and technology.

Often, however, the problem of economic improvement is fundamentally one of sociology, not technology. The would-be developer repeatedly encounters situations in which sociological obstacles prevent the adoption of a major technological change which would substantially improve economic output, and Sir Sydney cited as an example the production of rice in Ceylon. This could be increased substantially by major new technical developments of irrigation and opening up unused land, but much more substantially by the adoption by existing rice cultivators of better methods already proved elsewhere. The latter means would not have involved the considerable capital investment necessary for irrigation and land development, but propaganda and persuasion of a complex type, because the existing technique of growing rice is bound up with the whole way of life in villages, and affects family relations, inheritance and even religion, thus representing a long task for the sociologist as much as for the agricultural technician.

This illustrates the second broad aspect of the need for general education which Sir Sydney Caine emphasized. It is not sufficient for the directors or operators of development to be trained in matters other than technology: the general public with whom they deal also must be sufficiently well and broadly educated. In agriculture, as in all industrial or other advanced technological operations, a sufficient level of general education is essential; and in most under-developed countries the shortage of technicians and skilled craftsmen is the real obstacle to rapid economic development. Technology is not enough. Technicians and technologists must be educated in the social as well as in the natural sciences, and the mass of the population as well as the technical élite require general education.

Reviewing next the problems of education in the under-developed countries, Sir Sydney pointed out that only highly developed countries can afford general education in its modern form, and in starting from scratch in the under-developed countries the cost of technical education can be appalling. Moreover, the diversity of language constitutes a complication which can be a most serious obstacle, particularly as higher education is bound to make great use of languages foreign to the mass of the people, while mass education is necessarily conducted in the vernacular. The supply of text-books and periodicals is another great difficulty, especially at the university and postgraduate level; and the whole problem is often further aggravated by the emotional aspects of language. Sir Sydney did not hesitate to condemn the waste of time and effort, at a time when rapid progress in education is so urgent, caused by the multi-lingual education due to racial or national prejudice. Even without this, it is difficult indeed, with the great shortage of highly trained men and women, to induce enough of them to enter the higher levels of the teaching profession, and especially in those countries emerging to national status from Colonial dependence.

All this raises serious threats to the quality of education. In spite of the acute shortage of qualified local citizens for university or technical teaching, for example, emotionalism sometimes prevents effective use being made of outside assistance. Sometimes, too, it is assumed that if the right things are done, real incomes will rise and real wealth grow unprecedentedly quickly; and there is real danger of sacrificing quality to quantity and of so overloading the teachers that they become ineffective. Sir Sydney referred particularly to the danger of lowering standards of admission to universities. According to

a recent report from the University of Indonesia, of the 2,000 registered students in the Faculty of Engineering for the year in question, 1,300 were in the first year, a dozen or so in the fifth or final year and only one graduated.

The considerations noted by Sir Sydney imply that by its very nature the task of education for development must fall in the main upon the under-developed countries themselves, and in this connexion he stressed the importance of the 30,000 overseas students in the United Kingdom, the great majority of whom come from under-developed countries, while a high proportion of these are privately financed. Nevertheless, the developed countries have a most important part to play, particularly at the level of university and technical training, but their own specialized man-power difficulties set strict limits to what they can do; and Sir Sydney commented that the London School of Economics has every year to reject a high percentage of applications from abroad for higher degree studies because it has reached the limit of the numbers which its teaching staff can effectively supervise. The resources to be shared with the less advanced countries are not solely finances but above all highly trained men and women; and this is already being done by numerous agencies. Besides the great help given by British universities, through their organization as well as by offering places to overseas students, more than £29 million has been contributed during the decade 1946–56 by the British taxpayer to overseas students and education through the British Council and Colonial Development and Welfare Funds.

As the fruit of these and earlier efforts, there are now in British Colonies or former Colonial dependencies four universities, five university colleges and various other institutes of higher education. The Colombo Plan, which is essentially a collective name for various loosely co-ordinated pieces of mutual assistance by one Commonwealth country to another, has brought to numerous individuals in the under-developed areas opportunities of study overseas and grants of assistance to educational institutions. Commonwealth countries are also helping in ways quite outside the Colombo Plan, while many countries have received considerable aid to education under American foreign aid programmes. There is also the substantial help given by the Rockefeller Foundation and other private foundations, particularly for the initiation of new projects; and on the international plane much is being done through the Technical Assistance Board of the United Nations, through the United Nations Educational, Scientific and Cultural Organization and in specifically technical fields by the other specialized agencies such as the Food and Agriculture Organization and the World Health Organization.

Both the finance and technical personnel required for all this come in the main from the developed countries, and in this connexion Sir Sydney urged the importance of doing everything possible to ensure that British people who undertake a period of service abroad do not thereby damage their prospects for appointments in Britain. Something more could also be done to encourage the exchange of books and periodicals and the movements of scientists and other learned men. This is still liable to be hindered by political considerations even in non-Communist countries, and Sir Sydney fears that there is a danger of a system of exclusion of books and periodicals arising in non-Communist under-developed areas. Every effort should be made to assist people from under-developed countries to attend meetings of learned societies and to ensure that the problems of these countries receive attention at such meetings; Sir Sydney also suggested that the production in a single language appropriate to a particular area of summaries of scientific publications in diverse languages would be a very fruitful piece of international co-operation.

Such projects can scarcely become effective, however, unless the less-developed countries refrain from accentuating difficulties by exaggerating political, linguistic and psychological obstacles. If, however, the developed countries use to the full their opportunities for initiative in sharing their educational resources along such lines as Sir Sydney Caine indicates, that in itself would encourage the growth of mutual tolerance and goodwill. There would, nevertheless, appear to be a wide field in which professional societies could support what the universities and many educational institutions are already doing, not only to encourage the growth of such an atmosphere of goodwill, but also, and no less important, to assist the wisest and most effective use of the most precious of all resources, in developed and under-developed countries alike—that of trained men and women.

BIOLOGICAL RHYTHMS

At the sixth conference of the Society for Biological Rhythms, held on the Semmering, near Vienna, during August 26–28, thirty-six papers were presented by members and guests from eleven countries. They were welcomed by Dr. E. Dissmann (Klagenfurt), the local secretary.

The main theme of the opening session organized by Prof. A. Jores (Hamburg) was "Time in Biology", which was covered by six invited speakers. H. Laurell (Halmsted) critically discussed ancient and modern ideas of time, and contrasted its physical, physiological and psychological aspects; he also reviewed methods of measuring time. J. Aschoff (Heidelberg) elaborated the idea of time-cues or clues (*Zeitgeber*), namely, those periodical factors, external to a rhythmic system, which can be shown experimentally to control its phase. He demonstrated that in constant conditions of temperature and illumination and in the absence of noise or mechanical disturbance, 24-hr. patterns in the motor activity of vertebrates persist but gradually fall out of step, thus indicating that all external time-cues have been successfully eliminated. By reintroducing these potential cues one at a time their relative efficacy can be assessed. H. Kalmus (University College, London) observed that all life is accompanied by an incessant redistribution of material in space and time, and thus defined the investigation of biological rhythms as a study of the synchronization of mechanisms of transport. The appearance of any biological material at the 'right' time and at the 'right' site can be interpreted as a homœostatic arrangement brought about by the remote causes of selection, but must also be explained by the operation of physiological cues at any particular time. The opportunist nature of selection and the complexities of biological organization frequently produce non-optimal time adaptations and limited adaptability.

Dissociation of time-cues and internally established rhythms, such as those brought about by night work or air travel, may thus cause serious disturbances. Sir Nigel Ball (London) stressed the advantages, for bio-rhythmic studies, of plants over animals, in so far as the former lack the complications of a central nervous system. Using infra-red photographs he showed the extension growth of oat coleoptiles to be governed by a rhythm of approximately 24 hr. duration; this he could induce by transferring seedlings from light to darkness, and he could retard it by lack of oxygen. The rhythm persisted even after the removal of the tip of the coleoptile. In a more general way, Sir Nigel discussed the establishment and synchronization of rhythms in single elements and aggregates, and contended that the functional significance of the endogenous rhythms widely found in plants still remains obscure. F. Halberg (Minneapolis) surveyed many examples of physiological functions dependent upon time, and E. von Stockert (Rostock) gave a lively account of disturbances in the time sense and time consciousness of psychotic patients.

The six speakers at the opening session then formed a panel for a joint discussion of "Time in Biology", together with speakers from the floor. Also discussed was a lecture by J. Wilder (New York) concerning the relevance of that author's law of initial values for the interpretation of certain apparently rhythmic biological phenomena. J. Ježić (Sarajevo) claimed that, in the growth and decay of biological systems, cycles are best described by parabolas, and indicated some practical uses for such a concept.

The shorter papers of the later sessions were loosely grouped according to subject-matter or method. The 24-hr. periodicity of division in normal and malignant cells was discussed by F. Halberg, E. Halberg and J. J. Bittner (Minneapolis), and the implications for bioassay of daily fluctuations by F. Vering (Vienna). Daily fluctuations of bodily functions and their clinical importance were discussed by J. Blume (Düsseldorf), who exemplified the mathematical problems by analysing some of Kleitman's temperature curves during and after regimens in artificial light with periods of twenty-one and twenty-eight hours; W. Menzel (Hamburg) demonstrated variations in the interdependence in health and disease of the 24-hr. rhythm of rectal temperature, urine volume and concentration of chloride, urea and creatinine.

Ch. Kris (Cambridge, Mass.) presented results showing correlations between numerous performance tests and physiological measurements in respect of diurnal and menstrual rhythms, and described an objective measure of physiological age derived from her measurements. The biological age of man was also discussed by M. B. J. Nadel (Herzlia, Israel), and H. U. Ziolko (Berlin), who described disturbed day/night rhythms of vegetative functions in neurotic patients, and tried to explain some of their peculiar experiences during sleep as consequences of disturbed synchronization. S. Gifford (Boston) considered the developments of the pattern of sleep and wakefulness in infants from the point of view of a psychoanalyst, and T. H. Hellbrügge (Munich) treated the subject from the point of view of the physiologist. M. B. Ischlondsky (New York) dealt with the harm which may be caused by stimulation during 'inhibitory phases' of the human central nervous system, a factor which he holds responsible for many of the contemporary psychosomatic disorders. A. Topitz (Vienna) described one particular disturbance of rhythm, namely, that resulting from air travel in an eastern or western direction. After the Vienna Philharmonic Society's air journey to Tokyo it took its members about four days to become fully adapted to Tokyo local time. He reported similar experiences from several European athletes at the Melbourne Olympic Games.

Applying a principle first introduced by Möllerström to the insulin therapy of diabetes, H. G. Dennemark (Berlin) described clinical experiments demonstrating the importance for therapy of the hour of day at which various drugs and their combinations are administered in the treatment of hypertension.

L. Stark (Newhaven) considered nervous disorders such as tremor, ataxia or clonus as manifestations of inefficient servo-mechanisms. He gave a description of the working reflex to light of the pupil of the eye in terms of an automatic control device, and showed that certain pathological reactions he found in disseminated sclerosis could be understood by making simple assumptions concerning some parameters of an information loop. H. Drischel (Greifswald) described experiments in which he asked people to synchronize pairs of regular sequences of light flashes, acoustic clicks and taps on the finger tip. Transfer from the periodicity perceived with one sense to another was reasonably accurate within 5–15 hertz, but systematic errors occurred in certain transformations at specific frequencies.

The relation between respiratory, cardiac and vasomotor rhythms was discussed by several speakers: H. P. Koepfchen and K. Thurau (Göttingen) demonstrated curves indicating that the rhythms of vasomotor tonus and of respiration in the rabbit and dog are co-ordinated centrally at a frequency 1 : 1; but showed that other simple proportions of the rhythms occur in exceptional cases. K. Golenhofen (Berlin, Litchterfelde) showed that an analogous situation exists in man by comparing graphs of the rhythmic activity of the peripheral and central blood circulation, and H. Jordan (Bad Elster) demonstrated the presence in periodograms derived from human electrocardiograms of three rhythms, of 12, 28 and 60 sec. average duration, which he considered to be superimposed on the ordinary heart-rhythm.

Other statistical contributions included a paper by K. Freudenberg (Berlin), who presented an extensive collection of data on mortality disproving the belief in the biological importance of every seventh, fourteenth, twenty-first, etc., year of human life, and a paper by W. Otto (Falkensee) on annual fluctuations in birth weight. The possible importance of seasonal climatic factors, in particular of cold fronts, on asthma attacks and mental symptoms was discussed by S. W. Tromp (Leyden), who also expressed the hope that meteorological measurements during the current International Geophysical Year might profitably be correlated with detailed clinical observations.

Some fascinating glimpses into the homœostatic mechanics of rhythms were provided by G. C. Stephens (Minneapolis). Applying temperature changes to previously established light-controlled rhythms, as had been originally done by Kalmus, he analysed the 24-hr. movements of the melanophore pigment in the fiddler crab, *Uca pugnax*. Within the temperature-range 6–26° C., a 24-hr. melanophore periodicity

persisted in permanent darkness. The phases of induced rhythms could, however, be shifted by sudden changes in temperature provided these exceeded certain threshold values. Delays caused by extreme cooling persisted in darkness and were additive. Individual crabs in which melanophore rhythms of different phase had been induced kept them side by side when transferred to the same darkened aquarium. In spite of this independence of phase it was observed that the amplitude of the melanophore changes was increased by the presence of other fiddler crabs of the same or another species.

Among the papers circulated but not read, that by K. Hoffman (Wilhelmshaven) dealt with the influence of temperature and pretreatment on the 24-hr. motor activity of lizards; Y. Ondo's (Tottori, Japan) with the responses of shore sowbugs to the periodic movement of waves; E. Szirmay's (Budapest) described some uses of the comparative study of muscle rhythms, and L. S. Copelman's (Bucharest) dealt with some of the philosophical aspects of biological time.

The International Society for the Investigation of Biological Rhythms, to give it its original name, has now been in existence for twenty years, and at its six conferences a considerable part of the field has been surveyed. More recently the elaboration of general methods for the investigation of bio-rhythms and the formulation of a unifying theory have been attempted.

It is hoped that the full text of the papers will shortly be published. The Society has been invited by Dr. A. Caniggia (Siena) to hold its seventh conference in 1960 in Italy. Inquiries concerning the proceedings, membership and other matters should be addressed to Dr. A. Sollberger, Department of Anatomy, Karolinska Institutet, Stockholm.

H. Kalmus

FLAMMABILITY OF TEXTILES

In the past few years an increasing amount of publicity has been given to accidents resulting from the burning of clothing, and in the United States legislation has been introduced to prohibit the sale of certain very inflammable types of fabric. In the United Kingdom various safety committees have been set up, and a valuable report on the flammability of apparel fabrics in relation to domestic burning accidents has been published by the British Standards Institution*. It was not surprising, therefore, that the one-day conference, organized by the Textile Institute and dealing with the flammability of textiles, attracted a great deal of attention, for this was probably the first time that members of the textile industry, of the distributory trades and of the public were able to meet and discuss together the many aspects of the problem. The conference was held at the laboratories of the Rayon Research Association in Manchester on October 15, and was opened by the president of the Textile Institute, Sir Ernest W. Goodale.

It was evident from the substance of the four papers which formed the basis of the Conference that the seriousness of the high inflammability of certain textiles is widely appreciated and that the textile industry is anxious to overcome this hazard. Progress in dealing with the problem has in the past been hindered by lack of precise information, and perhaps the most important feature of the conference was the dissemination of reliable data to replace the lore which is often associated with anything that has to do with fire.

Mr. D. I. Lawson, of the Joint Fire Research Organization, summarized valuable data on the incidence of burning accidents, and his paper emphasized several unexpected observations. Of particular seriousness to the textile industry was the statement that burns involving clothing had the highest mortality-rate of any kind of burn, and that four out of five of the total accidents reported occurred in the home. This is in spite of repeated warnings of the danger from unguarded fires. It was indeed surprising to learn that only half the parents of young children questioned in an investigation had a fireguard. Mr. J. S. Ingham, of Messrs. Marks and Spencer, Ltd., who dealt with the economic aspects of fireproofing and with the possibility of being able to sell fire-proofed garments, also stressed the dangers associated with flared-out dresses and particularly with children's nightdresses made from winceyette.

All the speakers and many members of the conference agreed on the need for a publicity campaign to encourage the use of fireguards in homes where there are young children, and to popularize close-fitting night wear. Mrs. Jean Mann, M.P., speaking from the floor, suggested that the provision of fireguards should be made a condition of house letting.

The other solution, with which the textile and chemical industries are more directly concerned, is, of course, the provision of safe fabrics. It is difficult to define a 'safe' fabric, for the textile industry and the public must be in agreement about this. One of the first problems, therefore, is to devise a test for inflammability which has some relation to the practical hazards usually met with. Several of the suggested methods were discussed in detail by Mr. F. Ward, of Courtaulds, Ltd. Mr. Lawson thought that it would be unnecessarily stringent to define as safe only those fabrics which would not ignite when exposed to a radiant source of energy similar to that emitted from the surface of open fires. Measurement of the vertical speed of flame propagation was generally regarded as being more satisfactory because this gives the length of time available to extinguish the flame or to discard a burning garment. Apparatus for measuring this was described and the term 'flame resistance rating', defined as the time for flame to be propagated 100 in. vertically, was used for expressing the results obtained. Dr. T. H. Morton, of Courtaulds, Ltd., provided a great deal of useful information on how the flame resistance rating is affected by the composition, construction and weight of the fabric, and by the use of special processes, including some of the modern fireproofing finishes. There are many finishes which will reduce flammability, but for general acceptance other characteristics such as permanence of the proof and the feel of the cloth have also to be considered. There was general agreement that any proof used for children's nightdresses should give flame resistance throughout the life of the garment, that is, the effect should not be removed by as many as fifty washes.

Clearly one of the most difficult tasks is to define a safe value for the flame resistance rating. Mr.

* British Standards Institution: *PD* 2777 (1957).

Lawson suggested that a safe level should be well away from the level associated with the recent run of burning accidents, but not so high as to eliminate more types of fabric and flame retardant treatments than necessary. It was recommended that fabrics with a durable flame resistance rating of greater than 150 should be warranted as flameproof and identified as such. Most of the manufacturers of durable flame proofs are confident of being able to meet this standard, and many useful unproofed fabrics would be regarded as being safe.

The discussion by members of the conference was particularly stimulating, and included contributions from Dr. J. B. Bull, who has been intimately concerned with surveys made by the Burns Unit of the Medical Research Council, and from Mrs. Jean Mann, M.P., Mrs. F. P. A. McLaughlin, M.P., and Mr. Hervey Rhodes, M.P., all of whom are well known for their interest in the problems of safety and textiles.

The general conclusion from the conference was a unanimous agreement on the need for an intensified safety campaign at national level and for providing safe fabrics. Although many of the fabrics at present regarded as dangerous can be made safe by treatment with reagents such as tetra*bis*hydroxymethyl phosphonium chloride, antimony oxide, and mixtures of antimony and titanium oxides, it was recognized that a need still exists for cheaper durable treatments. Members of the conference, particularly the chemists and textile finishers, left greatly encouraged, knowing that the difficult problems with which they have to deal are sufficiently important to demand maximum effort and imagination. C. S. WHEWELL

THE ROCKEFELLER FOUNDATION

IN the Rockefeller Foundation annual report, 1956, the President's review, reprinted with a summary of the Appropriations Account and Principal Fund and a list of appropriations made in 1956, notes that for the year the appropriations totalled 30,075,305 dollars, the largest for any one year since the Foundation was established in 1913. Of this total, 5,963,605 dollars were for the humanities, 5,501,100 dollars for biological and medical research, 4,877,400 dollars for agriculture, 4,290,605 dollars for medical education and public health and 3,290,260 dollars for social sciences. For the fellowship programme, under which 458 individuals from 47 countries held fellowships in 1956, 2,025,000 dollars were appropriated.

In his review Dean Rusk stresses three features of the year's activities. First, noting that nineteen of the present eighty-one member States of the United Nations, with a population of more than 650 millions, have emerged as fully independent nations since the Second World War, he emphasizes that the officers and trustees of the Foundation believe that peace and orderly economic growth in the world during the next twenty-five years will be decisively influenced by what happens in these independent nations of Africa, the Middle East and Asia. Peace and stability will gain enormously if they establish constitutional systems with friendly and easy exchange with the rest of the world, increasingly productive economies, and educational systems which can train leaders in adequate numbers and educate their citizens for the responsibilities of their new societies. To enable the Foundation's expenditure on Latin America, Asia, the Middle East and Africa to be sharply increased without a large reduction of expenditure in the United States and Europe, the Trustees have decided to draw on capital funds for several years. During 1956 some 6 million dollars were allocated to the expanded programme, over and above the normal allocations to these areas from income.

Secondly, the President reviews at some length the Foundation's responsibilities in the nuclear age, commencing with its grant in 1940 toward the construction of a 184-in. cyclotron at the University of California, Berkeley. The report suggests that there are three main directions in which the resources of the Foundation can be usefully applied, taking into account the very large sums available from government and industry. The first is the public health aspects of nuclear energy, broadly conceived and for study of the effects of radiation on man. For the formulation of questions upon which further research is urgently needed the Foundation has already made grants to the National Academy of Sciences totalling 275,000 dollars. The second is in the Foundation's traditional support of basic scientific research with the main emphasis upon the living processes. Here, the nine grants for research in genetics made during the year totalled 991,000 dollars, the largest, 350,000 dollars, being to the University of Indiana, while 260,000 dollars went to the University of Copenhagen, 61,000 dollars to the National Centre for Scientific Research, Paris, 50,000 dollars to the Institute for Human Genetics, Upsala, and 24,000 dollars to the London Hospital Medical School. A third type of study for which Foundation support is planned, on a selective basis, is that of the economic, legal and political problems of the nuclear age, with special reference to the increasingly complex issues of international relations, with which nuclear energy is now inextricably bound up. About a dozen grants have been made to young professors in universities throughout the United States studying a wide range of contemporary political problems. The Foundation also hopes to assist a few mature scholars to embark on, or to complete, significant research in this field, to encourage institutes to undertake objective studies of international political problems, to stimulate the growth of organized knowledge and theories of foreign policy, including the techniques and principles involved in its conduct.

The third aspect of the year's activities emphasized by Dean Rusk is the assistance given to Hungarian scientists, scholars and students. To this refugee problem the Foundation in late 1956 and early 1957 devoted more than 1,200,000 dollars, almost 700,000 dollars of which went to the institutions in Austria which bore the brunt.

In the field of medical education and public health considerable attention was paid to professional education, grants for which included 367,400 dollars to the Christian Medical College, Vellare; 299,750 dollars to King George's Medical College, Lucknow; 273,300 dollars to Seth Gordhandas Sunderdas Medical College, Bombay; 570,000 dollars to the University of the Andes, Bogotá; 215,000 dollars to the Recife Medical School, Brazil; 290,000 dollars to the School of Medicine, Keio University, Tokyo; and 100,000 dollars to the Department of Child Health, University of Ankara. A grant of 163,280 dollars was made to provide four years support for studies of population dynamics in Indian villages jointly by Harvard

University and the Christian Medical College, Ludhiana, while one of 250,000 dollars to the Massachusetts Institute of Technology, for medical and biological research, was for the construction of a 1,000 kilowatt nuclear reactor at Boston, which would project a beam of nuclear rays into a therapy room underneath.

Some rather substantial grants of a general character made in 1956 were for the library at the international zoological station, Naples; for biological research at Amherst; for research in the natural sciences at the University of Mexico; and for biology, experimental medicine and surgery at Copenhagen. The largest of three grants for investigation of ways of meeting the nutritional requirements of children, especially during the critical years after weaning, was to the National Research Council and is being administered in close co-operation with the global programme of the United Nations Children's Fund. About 1,250,000 dollars were appropriated for field studies of viruses and basic research in virology. This included aid to collaborating groups.

In 1956 a further co-operative agricultural programme was started at the Indian Agricultural Research Institute, New Delhi, the first interests of which will be to improve the corn, wheat and other cereal crops and broad questions of advanced agricultural training and research. Under the Mexican co-operative programme, more than 400 young Mexicans and some 85 other young scientists from Latin America and the United States have received training. During 1956, 204 individuals from 30 countries received fellowships, scholarships or other study and travel grants in agriculture. Besides its participation in various types of international exchange in this field, such as the conference of 50 leading pathologists from Latin America, the United States and Canada on cereal rusts, the Foundation made numerous grants to institutions. These included 300,000 dollars to the College of Agriculture, University of Chile; 250,000 dollars to the College of Agriculture, University of the Philippines; and 200,000 dollars to the School of Agriculture, Universidade Rural de Minas Gerais, Brazil. A three-year grant of 153,600 dollars was made to the Harvard Graduate School of Public Administration to assist a seminar offering advanced training in new methods of water conservation and management.

In the social sciences, a grant of 98,400 dollars to the Computer Centre, Massachusetts Institute of Technology, was for further exploration of the uses of an advanced high-speed digital computer in solving theoretical and applied problems in the social sciences. A grant of 150,000 dollars to Vanderbilt University was for its Institute of Research and Training in the Social Sciences; of 114,000 dollars to Tulane University of Louisiana, for Latin American, legal and social studies; of 96,000 dollars to Stanford University, for its Food Research Institute; and of 50,000 dollars to the International Bank for Reconstruction and Development for its Economic Development Institute. The largest grant for international understanding in the United States in 1956 was one of 205,000 dollars over six years to the Harvard University Centre for Middle Eastern Studies, while 140,000 dollars went to the Federated Theological Faculty of the University of Chicago for inter-religious studies. The American University of Beirut received 216,000 dollars in continued support of its Arab studies programme.

ONTARIO RESEARCH FOUNDATION

REPORT FOR 1956

THE annual report of the Ontario Research Foundation for 1956* includes, besides the report of the director of research, Dr. H. B. Speakman, the financial statement and lists of papers published during 1956, with details of professional and technical staff, advisory committees, scholarships and post-graduate grants in science, 1956–57. In the Department of Biochemistry, where work for the tanning industry increased, progress was made in a group project on the production of sole leather with increased resistance to wear. The oils and fats laboratory has been investigating the production of a spread for use on Army biscuits, manufactured if possible from Canadian raw materials. It has also been studying the autoxidation of methyl isolinoleate, linoleate and oleate, using the Warburg respirometer, and the separation by gas chromatography of the volatile substances produced during the deterioration in flavour of fats and oils. A study of the fermentation of cheese whey was completed.

In the Department of Chemistry progress was made both in the development of methods for separating and determining different constituents of waste sulphite liquor and in evaluating the lignin components as sources of tanning agents and dispersing agents. Work also continued on the production of organic polymers, and the Foundation is supporting the design and construction of an atmospheric X-ray spectrometer incorporating an electron gun. Application of improved techniques developed for the analysis of condensed phosphates in fundamental studies of phosphate glasses, solutions and crystalline compounds led to the conclusion that there is a remarkable similarity in the dependence of the molecular-weight distribution of the glassy phases on their cation to phosphorus ratio.

Studies of the mechanism of fatigue failure of metals advanced considerably, and it was shown that a strong magnetic field affects the fatigue strength of ferritic metals. Basic research in the X-ray laboratory was concerned mainly with X-ray spectrographic studies, and more time was given to an investigation of the initial stages of oxidation on a metal surface.

In the work on parasitic nematodes, a minute nematode, *Aproctella stoddardi*, was recovered from a ruffed grouse, and is believed to account for one of the microfilariæ previously described as occurring in this bird. Low dosages of 'Daraprim' comparable to those effective against human malaria did not prevent infection from *Leucocytozoon simondi* developing in ducks, and particular attention was also paid to the relation between the time of infection and the prevalence of blood-sucking insects known to feed on ducks.

Work was commenced on the composition of the sand fraction from glacial tills and comparable water-laid sands, while studies continued on the relation between variety and yield of soybeans. In textile research, the Sigma Unevenness Tester, previously developed, was used in a survey of worsted yarns produced in Canada, and to a limited extent in the United States and Europe.

* Ontario Research Foundation. Annual Report, 1956. Pp. 31. (Toronto: Ontario Research Foundation, 43 Queen's Park, 1957.)

CARDIOTONIC ACTIVITY OF THE POTATO-ROOT EELWORM HATCHING FACTOR

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FOR many years it has been known that hatching of the potato root eelworm, *Heterodera rostochiensis* Wollenweber, takes place in response to a specific stimulus given off by the roots of the potato plant[1]: this 'hatching factor' is contained in the so-called potato-root diffusate. Attempts to isolate it have been made in Cambridge[2] and, more recently, in Groningen[3]; but although a good deal is known of its constitution, its exact nature is still unknown. The mechanism of its action is even more mysterious. Attempts to isolate the factor are severely handicapped by assay difficulties, for the only method is the hatching trial which, in its most commonly used form, is of three weeks duration[4]. It seemed highly desirable to attempt to find some preparation other than the eelworm which responds to the hatching factor; not only might this throw some light on the hatching mechanism itself, but it might also be of direct use as an assay method. The purpose of this article is to announce some initial success in both these directions.

It has already been shown that the hatching factor, eclepic acid[5], is probably a lactone acid of molecular weight about 300, containing an unsaturated lactone ring, a carboxyl group and two OH groups[6]. It seemed to us not unreasonable to assume that the activity might be associated with the lactone ring: it is well known that the lactones, particularly the unsaturated forms, include some of the most biologically active substances[7], and, in particular, that the cardiac glycosides, digitoxin, ouabain, etc., are among them. Moreover, it has already been shown that some, though not all, of the actions of cardiac glycosides[8–11] can be reproduced on the frog heart by simple unsaturated lactones. We have now found that the isolated frog heart responds to the hatching factor.

In general, the techniques used have been those of Giarman[9]. In some trials, the heart has been continuously perfused via the sinus, using the cannula he describes; more frequently, and in order to conserve our small supply of active substances, we have, like him, used a Straub preparation, cannulating the ventricle via the truncus. After perfusion in a Ringer solution, a hypodynamic state is induced by perfusion with a low-calcium Ringer solution; perfusion with a cardiotonic substance in low-calcium Ringer solution leads to a recovery. Fig. 1 shows the typical response to a series of dilutions of a concentrated preparation of the hatching factor.

Table 1. Relative Hatching Strength and Cardiotonic Activity

Preparation	Optimum hatching conc. (mgm./100 ml.)	Relative activity; hatching	Minimal cardiotonic conc. (mgm./100 ml.)	Relative activity; cardiotonic
G. 1	0·8	5·0	3	6·0
G. 2	2·5	1·6	5	3·6
Cambridge 'standard solid'	4·0	1·0	18	1·0

Almost all our work has been carried out with either of two concentrated preparations. One, 'standard solid'[2], was kindly given us by Sir Alexander Todd some years ago. For the other preparation, *G.*1, we are indebted to Dr. G. J. Janzen, of Groningen. With either preparation, the response varies with dilution, within certain limits; a more severe test, however, is the comparison of the two. The activities have been compared by the minimal concentration required to produce a detectable effect: the standard has its limitations, but the overwhelming necessity to conserve material has imposed this upon us. In the event, the comparisons have shown good agreement. The minimal concentration for the Dutch preparation is consistently 3 mgm./100 ml.; with the Cambridge standard solid, it is about six times greater. Since the recommended optimum hatching concentrations for these two preparations are 0·8 mgm./100 ml. and 4 mgm./100 ml., the agreement of the hatching and cardiotonic assessment is remarkable. The results are summarized in Table 1.

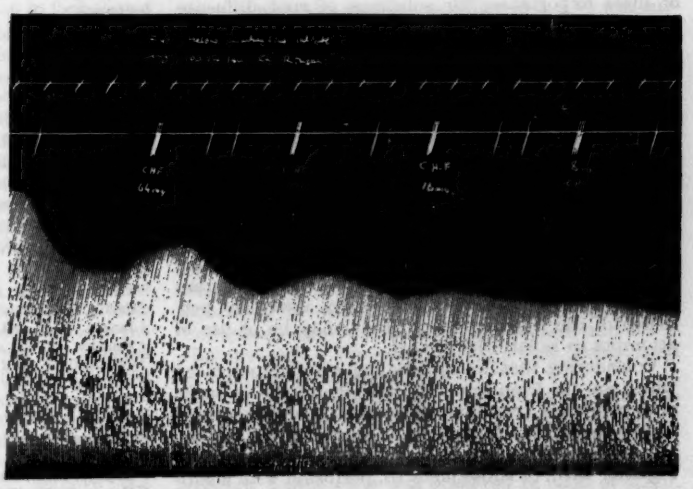

Fig. 1. Cardiotonic effect of hatching factor. Tracing begins with frog heart being perfused with Ringer, followed by low-calcium Ringer solution (single signal). Triple signals, from left to right, 64, 32, 16, 8 mgm. Cambridge 'standard solid' per 100 ml. low-calcium Ringer solution. Time signal, 30 sec. Straub preparation

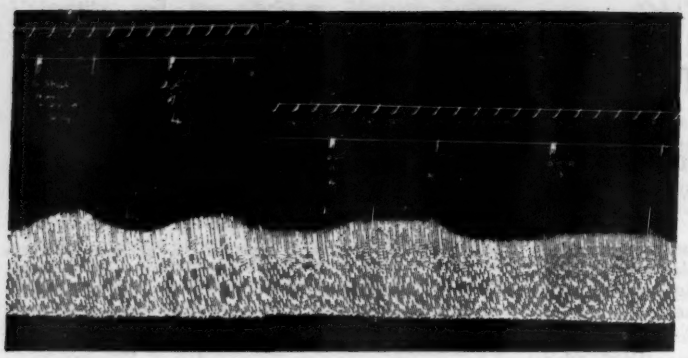

Fig. 2. 'Synergism' (see ref. 9) of hatching factor and strophanthin-*g*. Tracing begins with frog heart being perfused with low-calcium Ringer solution. First triple signal from left, 4 mgm. *G*.2 + 10 μgm. stroph.-*g*/100 ml. low-calcium Ringer solution: subsequent triple signals, respectively, 4, 4 and 3 mgm. *G*.2, all per 100 ml. low-calcium Ringer solution without strophanthin-*g*. Each stimulus is followed by low-calcium Ringer solution (single signal). Earlier tests in this same run had shown no response of the heart to any of these concentrations of *G*.2 or of 10 μgm. strophanthin-*g*. Time signal, 20 sec. Straub preparation

Very recently, however, we have carried out tests with two further Groningen preparations, *G*.2 and *G*.3; with these agreement has not been so good. As shown in Table 1, *G*.2 has a higher cardiotonic activity than its hatching assessment would suggest; nevertheless, it falls in its correct relative position. *G*.3 was the weakest preparation we have tested, its optimum hatching concentration being 5 mgm./100 ml.; and a sufficient quantity for tests with only ten hearts was available. In the event, the first run gave a reasonable agreement with the hatching assay, the minimal concentration being 54 mgm./100 ml.; however, no positive response was obtained with any of the other hearts. We have no explanation to offer for this; but we have evidence that this preparation may be unstable.

As an assay method for the hatching factor, perfusion of the frog heart has many limitations. The fact that it is far less sensitive than the eelworm is of little importance, for solutions of root diffusate are readily concentrated[12]. But the frog heart must be treated with ionic respect, and solutions obtained from potted potato plants will be quite unsuitable for perfusion; however, it has already been shown that it is not impossible to overcome this difficulty[3]; moreover, the Cambridge preparation has been assayed successfully in the present work, and this was obtained as a result of the first step in the attempt to isolate the factor, namely, absorption on charcoal and subsequent evaporation[2]. A more serious difficulty is the fact that the heart assay is unspecific—clearly the final arbiter of hatching activity must be the eelworm. Nevertheless, we are confident that, used with discretion, assay by perfusion of the hypotonic frog heart may be of use in attempts to isolate the factor.

Considering that we are dealing with preparations which are far from pure, the activity of the stronger ones compares very favourably with the more active simple lactones[9]. Moreover, as shown in Fig. 2, the minimal concentration can be halved by perfusion together with, or subsequent to, perfusion with a sub-minimal concentration of strophanthin-*g* (ouabain). A response at half the minimal concentration has also been obtained by perfusing the heart with the hatching factor plus a sub-minimal concentration of hydrogen peroxide. The 'synergism' with strophanthin-*g* and potentiation with peroxide are of particular importance, for they indicate that the responses obtained are indeed identical with those given by the pure lactones[6]. Moreover, it has been found that hydrogen peroxide also 'potentiates' hatching: addition of only 5 μgm. of peroxide per 100 ml. of a very dilute solution of hatching factor led to a doubling of larval emergence. Peroxide alone was without effect. Since many more larvæ emerged in identical drops of more concentrated hatching solutions alone, there can have been no shortage of oxygen as such which the peroxide made good.

The increased cardiac and hatching activity produced by the addition of traces of hydrogen peroxide to solutions of hatching factor strongly suggests that there are close similarities in the mechanisms involved.

The physiological activity of cardiac glycosides has recently attracted considerable attention, since certain of them have been shown to influence sodium–potassium transport in erythrocytes[13], frog skin (Johnson, V. K., personal communication) and isolated rabbit auricles (Weatherall, M., and Rayner, B., personal communication). Digitoxin has been shown to give rise to a peroxide in solution, and it has been demonstrated that, in this form, it may influence phosphorylation[14]. Simpler lactones may also have these actions: in fact, it was shown some years ago that they may behave as peroxides[11], and, more recently, it has been shown that certain of them may influence ion transport[15]. In the present work it has been demonstrated that the hatching factor has some of the properties of the cardiac glycosides and simpler lactones: if it should be shown that it influences the same fundamental physiological processes, not only will our understanding of the hatching mechanism be deepened, but also techniques of greater sensitivity and convenience may be available for its detection. These possibilities are being explored.

We are indebted to Prof. A. D. Hobson for his support, and wish also to thank Sir Alexander Todd, of Cambridge, and Dr. G. J. Janzen, of Groningen, for their interest and co-operation. The work was made possible by a grant from the Nuffield Foundation, to which we wish to express our thanks.

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AMINO-ACID COMPOSITION OF THE SIX HISTONES OF CALF THYMOCYTES

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EARLIER work[1] from this laboratory established that the histones present in the cell nuclei of many species and tissues are composite in character, all of them containing a main and one or more subsidiary histones. The former, which constituted the major component, was characterized by a relatively small solubility in aqueous alcohol and a high arginine content; its general amino-acid composition was, indeed, typical of the traditional histones of the older literature. The subsidiary histones were more soluble, and, with one exception, were distinguished from the main component by their low content of arginine. Despite their deficiency in this amino-acid, they nevertheless exhibited strong basic properties. By examining an extensively fractionated specimen of a subsidiary histone from the thymocytes of the calf it was ascertained that, for this particular histone, these strong basic properties were due to a very high content of lysine. It was also characterized by a high content of alanine and proline and by the absence of phenylalanine, tyrosine and histidine[2]. The indication that it contained a minute amount of methionine is now known to have been incorrect, for this amino-acid could not have survived the conditions under which the chromatogram in which it was detected was prepared.

The existence of subsidiary histones rich in lysine and alanine in the thymus gland of the calf has since been confirmed by several groups of workers[3–7]. In the meantime, the results of our electrophoretic and ultracentrifugal studies of various histones had convinced us that all the subsidiary histones hitherto examined were actually mixtures of closely related proteins which had so far defied all attempts at complete separation. Such studies[8] had in fact shown that the total histone from the thymus gland of the calf and the liver of the ox consisted of six components which were designated α_1, α_2, α_3, β, 1·6 *S* and 0·8 *S* γ-histones. Of these, the first three replace the α-histone and the last two the γ-histone of our earlier nomenclature[9]. Such changes were rendered necessary by the discovery that the original α- and γ-components could be resolved into five histones. The three α's differed in their electrophoretic mobilities, while the two γ's possessed nearly identical electrophoretic mobilities although they differed in their sedimentation constants.

The physical characterization of these various components rendered possible attempts at their separation. The first step in this direction was the preparation from the total histones of the thymus gland of the calf of the crude α-fraction which, despite its name, actually comprised the three α-histones and the 0·8 *S* γ-histone. The further stages of fractionation presented, however, many difficulties. For various reasons, both ion exchange and adsorption (alumina) chromatography failed to achieve the desired results. Using the former method with the resin '*IRC*-50' (generously given by the Rohm and Haas Co., Philadelphia) according to the procedure of Crampton, Moore and Stein[5], two fractions *A* and *B*, corresponding with their results, were obtained. But when fraction *A* was examined electrophoretically it was found to consist of a mixture of α_1- and α_2-histones. In their recent work[10], Crampton, Stein and Moore have also been led, on other evidence, to suspect the homogeneity of their preparations.

Much greater success in the separation of the α-fraction has been achieved by zone electrophoresis. Using a medium of starch with veronal buffers at *p*H 8·5 and of ionic strength 0·18 a substantial separation of the above α-fraction into the four components has been effected. In the procedure adopted, the influence on the results of the tailing observed during the electrophoresis of histones on paper or in a starch medium, which is caused by the binding of the positively charged histones to the negatively charged surfaces of the medium, was largely swamped by using high concentrations of the α-fraction. A current of 40 m.amp. was passed through the starch in the trough, which had a cross-sectional area of 17·6 cm.^{2}. The trough was immersed in ice-cold water and kept in a cold room at 2° C. Electrophoresis was carried out for 80 hr., a time suggested by pilot experiments. A print on filter paper was then taken from the surface of the starch block. After staining, this indicated the presence of four bands. Four sections corresponding with the positions of these bands were then cut from the starch block and extracted separately with 0·1 *N* sulphuric acid. The extracts were then neutralized with sodium hydroxide and lyophilized. Of the four products so obtained, the one with the smallest mobility (0·8 *S* γ) was submitted to a second run. The product was electrophoretically homogeneous, but when examined by sedimentation was found to be contaminated with the 1·6 *S* γ-histone. This was accordingly removed by preparative ultracentrifugation in 20 per cent aqueous alcohol at *p*H 9·0 and the 0·8 *S* γ-histone sulphate precipitated from the acidified mother liquors with excess of alcohol. The product now sedimented as a monodisperse substance at *p*H 8·5 with a sedimentation coefficient of $0·83 \times 10^{-13}$. The quantities of the remaining three fractions available were unfortunately too small for further purification by zone electrophoresis. The four products were therefore dissolved separately in small volumes of water and dialysed in 'Cellophane' sacs successively against water and 0·1 *N* sulphuric acid. The sulphates were then precipitated by addition of 12 vol. acetone.

When examined in the Tiselius apparatus the fastest three fractions were found to possess mobilities corresponding with α_1-, α_2- and α_3-histones, although evidence of the presence of small amounts of the adjacent components was observed in each of them. It was calculated, for example, from the pattern of the α_1-component that the impurity amounted to

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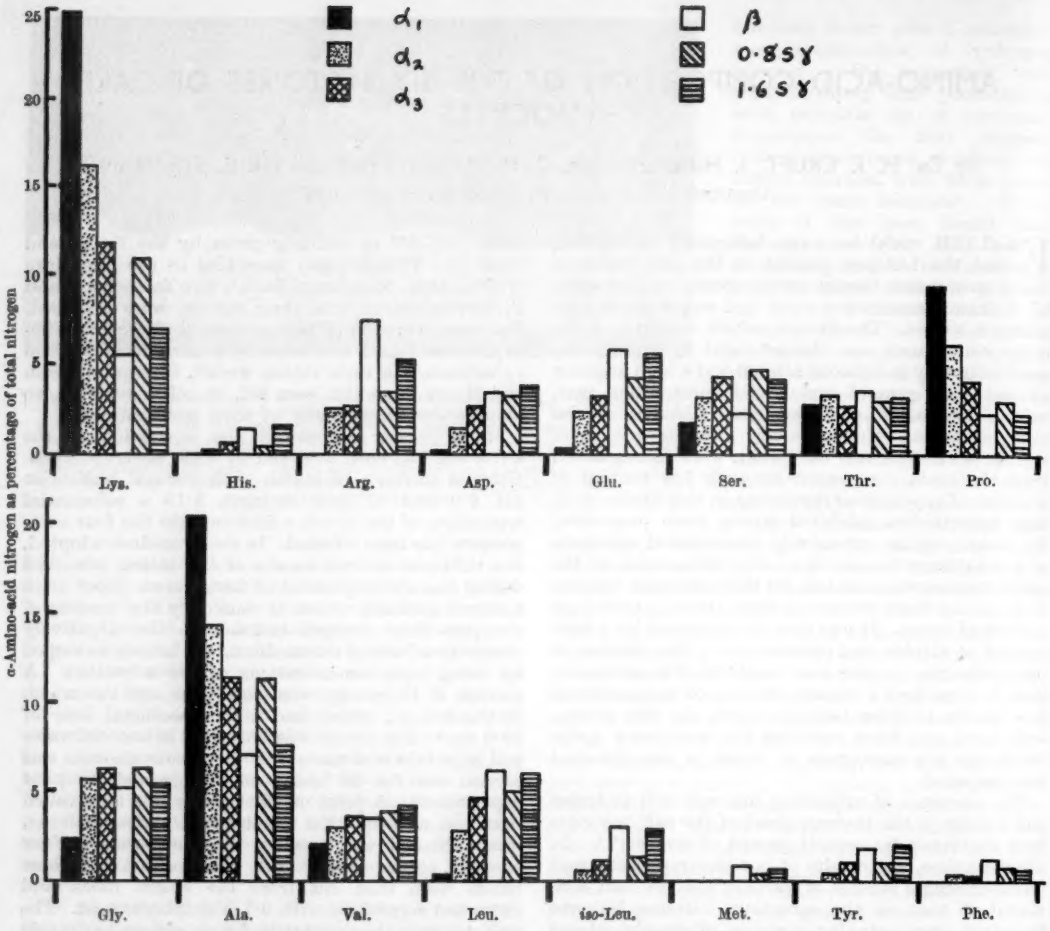

Fig. 1. The amino-acid composition of the six histones from calf thymus glands expressed as α-amino-acid nitrogen as a percentage of the total nitrogen. The more usual figures of amino-acid nitrogen as a percentage of the total nitrogen can be obtained by multiplying the values for lysine, histidine and arginine by 2, 3 and 4 respectively

10–15 per cent of α_3. Sedimentation coefficients were also determined in the Spinco ultracentrifuge. The values obtained were: α_1-histone, $0{\cdot}45 \times 10^{-13}$; α_2-, α_3- and 0·8 *S* γ-histones, $0{\cdot}8 \times 10^{-13}$. Since the diffusion coefficient of the crude α-fraction is about 8×10^{-7}, this suggests molecular weights for the α_2-, α_3- and 0·8 *S* γ-histones of the order of 10,000, and of about half that figure for the α_1-histone. Of the four preparations, the α_3-histone proved to be the most heavily contaminated with impurity, for the sedimentation experiments revealed that this contained about 30 per cent of β-histone. The presence of β-histone in this component and of the 1·6 *S* γ-component in the original 0·8 *S* γ-histone despite their preparation from material containing no detectable amounts of these histones was doubtless due to the large losses during dialysis of the α- and 0·8 *S* γ-fractions. This, combined with the electrophoresis, resulted in the concentration of the negligible proportions of β- and 1·6 *S* γ-histones in the original α-fraction into readily detectable amounts in the above preparations.

The four preparations described above were obtained in insufficient amount for further purification. They were, however, all analysed for amino-acid composition. The results are presented graphically in Fig. 1, in which have also been included the figures obtained in unpublished work for pure β- and 1·6 *S* γ-histones. In calculating the results of the analyses of the α_3-histone, we have corrected the values for the presence of 30 per cent of β-histone.

Attention should be directed to the fact that the ordinates in Fig. 1 represent amounts of α-amino nitrogen expressed as a percentage of the total nitrogen. This unusual method of recording the amino-acid composition of proteins has been adopted in this case because it enables a direct comparison to be made between the number of cationic groups present in the various histones. Moreover, the figures are proportional to the number of moles of amino-acid per mole of protein.

Consideration of the above results will show that they provide a complete confirmation of the previous work which has been carried out in this laboratory

on the composite nature of the histones obtained from the thymocyte of the calf. In particular, they confirm: (1) the presence of the six components shown to be present by physicochemical methods[8]; (2) the strongly basic properties of all of them[8]; and (3) the presence of high quantities of lysine, alanine and proline[8] in many of the subsidiary histones. In addition to this, however, they serve to correlate the electrophoretic mobilities of the histones with their amino-acid composition. Thus, the number of cationic groups per 100 gm. of protein nitrogen present in the six compounds, arranged in order of mobility, are: $\alpha_1 = 24{\cdot}7$; $\alpha_2 = 18{\cdot}6$; $\alpha_3 = 15{\cdot}1$; $\beta = 14{\cdot}3$; 0·8 *S* $\gamma = 14{\cdot}2$; 1·6 *S* $\gamma = 13{\cdot}9$. It should be added that the two γ-components possess almost identical mobilities, and that, while the β exhibits a greater mobility than the 1·6 *S* γ-histone despite their containing virtually identical numbers of cationic groups, this apparent slight discrepancy is explained by the greater number of free carboxyls present in the latter[8].

All the components resemble one another in being devoid of tryptophan, cysteine and cystine; the α's are, however, distinguished from the others by the absence of methionine. Of the six histones, α_1 is the simplest, containing only the seven amino-acids lysine, alanine, proline, serine, threonine, glycine and valine. If one excludes simple peptides from the comparison, α_1-histone is probably unique among known proteins in containing no arginine. α_3 differs qualitatively from α_1 in containing the four additional amino-acids arginine, leucine, glutamic and aspartic acids. The remaining components possess more complex compositions than do α_1 and α_3.

The conclusive demonstration in this and former communications from this laboratory of the composite nature of the histone present in the thymus gland of the calf clearly renders obsolete the many analyses of this protein recorded in the literature[11], for it is evident that the preparations to which these refer must have been unknown mixtures of two or more of the above components.

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EFFECTS OF SARCOMYCIN ON THE METABOLISM OF EHRLICH ASCITES CARCINOMA CELLS

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UMEZAWA *et al.*[1] have found that an antibiotic, sarcomycin, produced from *Streptomyces erythrochromogenes*, shows anti-tumour activity against Yoshida rat sarcoma and Ehrlich carcinoma in mice. Hooper *et al.*[2] have shown that the chief active constituent of sarcomycin is 2-methylene-3-oxo*cyclo*pentane-carboxylic acid, the hydrogenated form of which (2-methyl-3-oxo*cyclo*pentane-carboxylic acid) lacks antibacterial activity but is highly active against Ehrlich ascites tumour. Clinical trials by Magill *et al.*[3] have indicated that sarcomycin is without appreciable therapeutic value in disseminated cancer, although Ishiyama[4] reported some favourable effects. In view of the definite activity of sarcomycin against Ehrlich ascites carcinoma, we have investigated the effects of sarcomycin on the metabolism of this tumour, using a preparation generously provided by Bristol Laboratories, Inc., Syracuse, N.Y.

Our investigations have involved a study of the effects of sarcomycin on the rate of respiration and of anaerobic glycolysis of Ehrlich ascites carcinoma cells, on the uptake of glycine-1-^{14}C into the tumour cells, on the incorporation of radioactivity from glycine-1-^{14}C into the tumour proteins and on the incorporation of phosphorus-32 (from radioactive phosphate) into the adenosine mono-, di- and tri-phosphates, ribonucleic acid and deoxyribonucleic acid of the tumour.

All studies were carried out *in vitro* with washed Ehrlich ascites carcinoma cells obtained from Swiss white mice after intraperitoneal injection. Ascitic fluid was withdrawn with a hypodermic syringe after six days, and the cells were separated by centrifuging at room temperature and washed three or four times with 8–10 volumes of cold isotonic saline to remove blood elements and soluble ascitic constituents.

The conventional Warburg manometric apparatus was used for estimating respiratory and glycolytic rates and for the incubations in which the uptake and incorporation of glycine-^{14}C or phosphorus-32 were studied. The Ringer media used were those described by Umbreit *et al.*[5]. Aerobic experiments were carried out by incubation at 37° in an atmosphere of air or oxygen, potassium hydroxide being placed in the centre wells of the manometer flasks for absorption of carbon dioxide; anaerobic experiments were carried out in an atmosphere of 93 per cent nitrogen and 7 per cent carbon dioxide.

For estimation of glycine uptake and incorporation by the ascites cells, glycine was tipped from the side tube of the manometer vessel (after gassing and thermal equilibrium) so that the final concentration in the total volume of 3 ml. in the manometer flask was 2 *mM* and contained glycine-1-^{14}C to give an activity of 10^5 counts per min. (0·67 μc.). After incubation, the manometer vessels were placed in

crushed ice, their contents (cells and medium) were homogenized in a Teflon pestle homogenizer, precipitated with trichloracetic acid (final concentration 13 per cent) and further homogenized. The precipitates were extracted three times with 6 per cent trichloracetic acid (first extraction carried out for 15 min. at 90° C. to remove nucleic acids), once with ethanol, once with ethanol–ether (3 : 1) at 60° C. for 10 min., once with ether, and finally the residual proteins were suspended in chloroform–ether (4 : 1), plated on aluminium disks and counted. Uptake of glycine-1-^{14}C into Ehrlich ascites carcinoma cells was estimated after incubation of the washed cells for 30 min. at 37° C. in the appropriate media. The contents of the manometer vessels were transferred to centrifuge tubes kept in crushed ice and centrifuged for 1 min. The packed ascites cells were resuspended in 5 ml. ice-cold 0·1 *M* glycine (non-radioactive) and centrifuged for 1 min. The cells were then resuspended in 2 ml. 95 per cent ethanol, kept at room temperature for 2 hr. and centrifuged. An aliquot (0·5 ml.) of the supernatant solution was plated and counted. From this count the concentration of free glycine in the ascites cells was calculated.

For estimation of phosphorus-32 incorporation into Ehrlich ascites carcinoma cells, the washed cells were packed by centrifuging and suspended in a total of eight times their own volume of Ringer solution containing no added buffer. 1·0 ml. of the suspension was used per vessel for incubation with radioactive phosphate. The final incubation medium (3 ml.) contained Ringer solution[5], 0·01 *M* phosphate buffer *p*H 7·4 with or without glucose or sarcomycin. The side arm contained approximately 0·1 mc. phosphorus-32 as carrier-free phosphate which was tipped in after the 10-min. period allowed for attainment of thermal equilibrium. At the end of a 30-min. incubation period in air at 37° C., the contents of the vessel were removed with a Pasteur pipette and added to 5 ml. of a Ringer solution containing no buffer. The ascites cells were separated by centrifuging, the supernatant was discarded and the cells washed with a further 8 ml. of buffer-free Ringer solution. They were then resuspended in 1 ml. water, precipitated with 6 ml. 95 per cent ethanol and allowed to stand for 30 min. to ensure complete precipitation. After centrifuging, the supernatant was decanted and subjected to chromatography and autoradiography as described by Bolton *et al.*[6]. In this way the activities of the adenosine mono-, di- and tri-phosphates were assessed.

The alcohol-insoluble residue was washed with two lots of 5 ml. 5 per cent trichloracetic acid, made up to 2 ml. with *N* potassium hydroxide, incubated for 18 hr. at 37° C., and an aliquot plated and counted[7]. This gave a value for the combined deoxyribo- and ribo-nucleic acids and phosphoprotein fractions. To the remaining solution was added 6 ml. *N* hydrochloric acid to precipitate the deoxyribonucleic acid fraction, and the material was maintained at 0° C. for 90 min. The deoxyribonucleic acid was removed by centrifuging and washed with two further portions of 8 ml. *N* hydrochloric acid. The washed deoxyribonucleic acid fraction was suspended in 0·5 ml. water, and 0·2-ml. aliquots were plated and counted.

Sarcomycin, at concentrations up to 200 μgm./ml., has little or no effect on the rate of oxygen consumption of Ehrlich ascites carcinoma cells either in the presence or absence of glucose. Some typical results are given in Table 1. Nor does sarcomycin at such concentrations affect the rate of anaerobic glycolysis. When the concentration of sarcomycin is increased, however, to 600 μgm./ml., relatively large inhibitions of the rates of respiration and glycolysis take place. For example, at 670 μgm./ml. sarcomycin brings about 63 per cent inhibition of the rate of oxygen uptake of Ehrlich ascites carcinoma cells in absence of glucose, and 51 per cent inhibition in presence of glucose; the rate of anaerobic glycolysis is inhibited 33 per cent. Such inhibitive effects of sarcomycin at 670 μgm./ml. are not seen on the respiratory or glycolytic rates of chick embryo (four days old) or on rat spleen slices.

Table 1. Effects of Sarcomycin on Metabolism of Ehrlich Ascites Carcinoma Cells and on Incorporation of Glycine-1-^{14}C into the Tumour Proteins

Incubation of washed Ehrlich ascites carcinoma cells was carried out aerobically in the conventional Warburg manometric apparatus for 30 min. at 37°. The Ringer solution, in which the tumour cells were suspended, contained 2 m*M* glycine in which glycine-1-^{14}C, having an activity of 10^5 counts per min. per vessel, was present

	No sarcomycin added	Sarcomycin added (200 μgm./ml.)
Q_{O_2} (no glucose added)	13·6	10·8
Q_{O_2} (in presence of 0·02 *M* glucose)	7·8	6·8
Glycine-1-^{14}C incorporated into tumour proteins (no glucose added)	86 counts/min./mgm. protein	26 counts/min./mgm. protein
Glycine-1-^{14}C uptake into the tumour cells (no glucose added)	11,100 counts/min./vessel	8,500 counts/min./vessel
Glycine-1-^{14}C incorporated into tumour proteins (in presence of 0·02 *M* glucose)	96 counts/min./mgm. protein	34 counts/min./mgm. protein
Glycine-1-^{14}C uptake into the tumour cells (in presence of 0·02 *M* glucose)	10,000 counts/min./vessel	8,700 counts/min./vessel

Sarcomycin, at 200 μgm./ml., brings about marked diminutions in the rates of incorporation of glycine into the tumour proteins, typical findings being shown in Table 1. Moreover, it will bring about, at this concentration, an inhibition of the rate of anaerobic incorporation of glycine, in the presence of glucose, amounting to 64 per cent, a value which may be compared with that of 80 per cent brought by sarcomycin on the rate of aerobic incorporation of glycine in the absence of glucose. Higher concentrations of sarcomycin (for example, 670 μgm./ml.) bring about more than 90 per cent inhibition of the rates of incorporation of glycine into Ehrlich ascites tumour protein both under aerobic conditions (in presence or absence of glucose) or anaerobic conditions (in presence of glucose). Incorporation of glycine into the proteins of chick embryo (four days old) or rat spleen slices is also affected by the high concentration of sarcomycin (670 μgm./ml.); but the inhibitions, which may be of the order of 70 per cent, are not so great as those found with Ehrlich ascites tumour cells. The rate of uptake of free glycine into the Ehrlich ascites cells is but little affected by sarcomycin at 200 μgm./ml., as shown in values given in Table 1. It is evident that the marked inhibitions of the rates of glycine incorporation into the tumour proteins by sarcomycin, at 200 μgm./ml., are not due to an interference with the rate of transport of the amino-acid into the tumour cells. Moreover, it is clear that sarcomycin exceeds in potency, so far as inhibition of glycine incorporation into Ehrlich ascites tumour proteins is concerned, the series of compounds having antitumour activities investigated by LePage and Greenlees[8]. Roberts *et al.*[9] have suggested that sarcomycin might effect its

antitumour activity by interference with an aspect of glutamine metabolism. We have not found, however, any reversing action of L-glutamine on the inhibition by sarcomycin of the incorporation of glycine-1-^{14}C into Ehrlich ascites carcinoma proteins.

It is now known that incorporation of amino-acid into protein requires the participation of adenosine triphosphate[10], the stimulating effect of adenosine phosphates on the incorporation of amino-acid into proteins in cell-free liver extracts having been established[11]. Rabinovitz *et al.*[12] have demonstrated that incorporation of amino-acid into the proteins of Ehrlich ascites carcinoma cells takes place aerobically and anaerobically in presence of glucose. Dinitrophenol (5×10^{-5} *M*) inhibits aerobic incorporation of amino-acids and at the same time stimulates oxygen consumption; but it has little effect on glycolysis-linked incorporation. Thus the dinitrophenol does not inhibit the incorporative mechanism directly, but it depletes the necessary energy supply[12], presumably adenosine triphosphate.

In view of these facts and the demonstration that sarcomycin inhibits the incorporation of glycine into the protein of ascites carcinoma cells, investigations were carried out to discover the effect of sarcomycin on the incorporation of phosphorus-32 into the adenosine phosphates and into the ribo- and deoxyribo-nucleic acid fractions. It is already known[13] that compounds having antitumour activities can affect the incorporation of phosphorus-32 into the nucleic acids of mouse tumours.

Our results, given in Table 2, show that the presence of glucose markedly increases the incorporation of phosphorus-32 into adenosine di- and tri-phosphate and ribonucleic acid in Ehrlich ascites carcinoma cells incubated aerobically for 30 min. at 37°; little enhancing effect is seen with adenosine monophosphate or deoxyribonucleic acid. They also show that sarcomycin (200 μgm./ml.) greatly reduces the incorporation of phosphorus-32 into adenosine di- and tri-phosphate and the ribonucleic acid fraction in the absence of glucose, the inhibitions amounting to about 50 per cent. Finally, they show that, in the presence of glucose, sarcomycin suppresses the incorporation of phosphorus-32 into adenosine mono-, di- and tri-phosphate and the ribonucleic and deoxyribonucleic acid fractions, the inhibitions amounting to about 70 per cent except in the case of the last fraction. This suppression of incorporation of phosphorus-32 is not due to an inhibition of the rate of transport of phosphate into the ascites cells. In the experiment described in Table 2, phosphorus-32 uptake into the ascites cells amounted to 134,000 counts per min. and in the presence of sarcomycin (200 μgm./ml.) the uptake amounted to 112,000 counts per min. The results point, therefore, to an interference by sarcomycin with the reactions of the adenylic acid system and could be explained either by an inhibition of the rate of formation of adenosine triphosphate or by an increased rate of breakdown of that substance. The inhibitions are of the right order to account for the suppression of incorporation of glycine-1-^{14}C by sarcomycin if this incorporation is dependent on the rate of phosphate turnover in the adenine nucleotides and nucleic acids. This conclusion is supported by the fact that anaerobic incorporation of amino-acids into ascites proteins takes place to a marked extent only in the presence of glucose[12] and by the observation (Creaser, E. H., and Scholefield, P. G., unpublished work) that incorporation of phosphorus-32 anaerobically into the adenine nucleotides and nucleic acids in Ehrlich ascites carcinoma cells is very greatly increased (more than twenty-fold with adenosine di- and tri-phosphate) by the presence of glucose.

Table 2. Effects of Sarcomycin on Incorporation of Phosphorus-32 into Adenosine Phosphates, Ribonucleic Acid and Deoxyribonucleic Acid of Ehrlich Ascites Carcinoma Cells

Incubation of 0·125 ml. packed washed Ehrlich ascites carcinoma cells in 3 ml. isotonic Ringer solution was carried out aerobically for 30 min. at 37° C. in the conventional Warburg manometric apparatus. The Ringer solution contained 34·3 μmoles radioactive phosphate equivalent to 12×10^6 counts per min. of phosphorus-32

Additions to suspension of Ehrlich ascites tumour cells	Incorporation of ^{32}P (counts per min. × 10^3) into: AMP	ADP	ATP	RNA fraction	DNA fraction
Nil	2·25	16·9	7·80	4·7	0·98
Glucose 0·02 *M*	2·86	32·4	26·0	10·3	1·27
Sarcomycin 200 μgm./ml.	3·25	7·0	3·27	2·4	0·60
Glucose, 0·02 *M* plus sarcomycin, 200 μgm./ml.	1·4	13·5	9·9	3·2	0·75

The mechanism by which sarcomycin effects its disturbance of the reactions of the adenylic acid systems is still obscure. Although the disturbance resembles the 'uncoupling' action of dinitrophenol, the behaviour of sarcomycin differs markedly from that of the latter. The most obvious differences are: (1) lack of stimulation of the rate of oxygen consumption of ascites cells which is a characteristic feature of dinitrophenol activity, (2) marked inhibition of glycine-1-^{14}C incorporation anaerobically in presence of glucose, in contrast to the feeble (or lack of) inhibition exercised by dinitrophenol under the same conditions (ref. 12, and Bickis, I. J., and Quastel, J. H., unpublished work).

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LETTERS TO THE EDITORS

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Combined Light and Velocity Measurements of the Variable Star 12 Lacertae

During the summer and autumn of 1956, fifteen observatories co-operated in securing brightness and radial velocity measurements of the variable star 12 Lacertae. The variable belongs to the group of Beta Canis Majoris stars, consisting of about a dozen known members, which vary in light and radial velocity. Stars of this group have spectral types *B*2, *B*3, and luminosity classification II–IV, and their periods range between 0·15d. and 0·25d. The amplitudes of the light curves are small, of the order of some tenths of a magnitude. The light and radial-velocity curves are often not quite regular, showing that they are the result of several components. Thus the star 12 (*DD*) Lacertae has a principal period of 4h. 38m. and a secondary period of 4h. 44m., while recently a third component of 3h. 45m. has been found, and a fourth one of 3·9h. has been suggested. The periods occur in the variation of both the light and the radial velocity. The presence of components with closely similar periods and amplitudes of the same order produces the beat phenomenon, characteristic of a number of stars of the Beta Canis Majoris group. The occurrence of this relatively large number of components produces the observed complexity of the light and velocity curves.

The derivation of these components from scattered observations obtained at a single site is difficult, because of the small amplitude of the light curve and the complexity of its character. Too much information is lost during the time when the star is not under observation.

Accordingly, a plan was undertaken to obtain more information about 12 Lacertae, a typical member of the group, by combining observations made at sites distributed around the world at northern latitudes between 30° and 60°. Although regular observations were arranged for the period July–December 1956, the main effort was to observe the star continuously during the fourteen days between August 28 and September 12. A smaller number of observatories participated in increased observing activity between September 27 and October 12.

This campaign was successful on the whole, although we did not succeed in keeping the star under continuous observation during one complete fortnight, mainly because of the facts that, of the three Asiatic observatories which had intended to co-operate, those at Naini Tal (India) and Nanking (China) could not join the campaign because of continuous bad weather and of instrumental difficulties, and owing to bad weather Tokyo Observatory was able to make a good series of observations on one night only and secured some scattered observations during three other nights. The observations were finally made at fifteen observatories, including seven in Europe, seven in America and one in Asia. The distribution of the observing time is given in Table 1.

Table 1

	Aug. 28–Sept. 12	Sept. 27–Oct. 12	Outside these periods	Total
Photoelectric brightness observations	296·4 hr.	128·3 hr.	139·9 hr.	564·6 hr.
Radial velocity observations	143·0 hr.	—	10·5 hr.	153·5 hr.
				718·1 hr.

The number of observations and their density in time are such that our campaign may certainly be called successful. That fairly continuous observation of the star was possible at least during part of the period is shown by *Fig. 1*, giving the resulting light-curve in the Julian day intervals 2,435,720·3–2,435,721·8 and 2,435,722·2–2,435,723·8.

In order to plot the various observations to the same scale of magnitudes, the relative zero-point corrections of the different magnitude scales were determined by comparing all overlapping parts of the light-curves. In this way a system of twenty-five equations with twelve unknowns was obtained, and solved by the method of least squares. The scales of the various sets of observations appear not to differ by more than some hundredths of a magnitude. The magnitude scale of the accompanying figures is that used at the Simeis Observatory (Crimea, U.S.S.R.). The figures clearly show the semi-regular shape of the light curves and demonstrate how difficult it would have been to infer such irregularities from observations at one site taken during 0·3-day periods at intervals of one or more days.

The further reduction of the observations, including the colours and the radial velocities, will be carried out by one of us (C. de Jager) and will be published elsewhere.

We are grateful to Prof. O. Struve (Berkeley, U.S.A.) and also to Prof. B. V. Kukarkin (Moscow, U.S.S.R.), president of the Commission for Variable Stars of the International Astronomical Union, for their stimulating advice and support in preparing this campaign.

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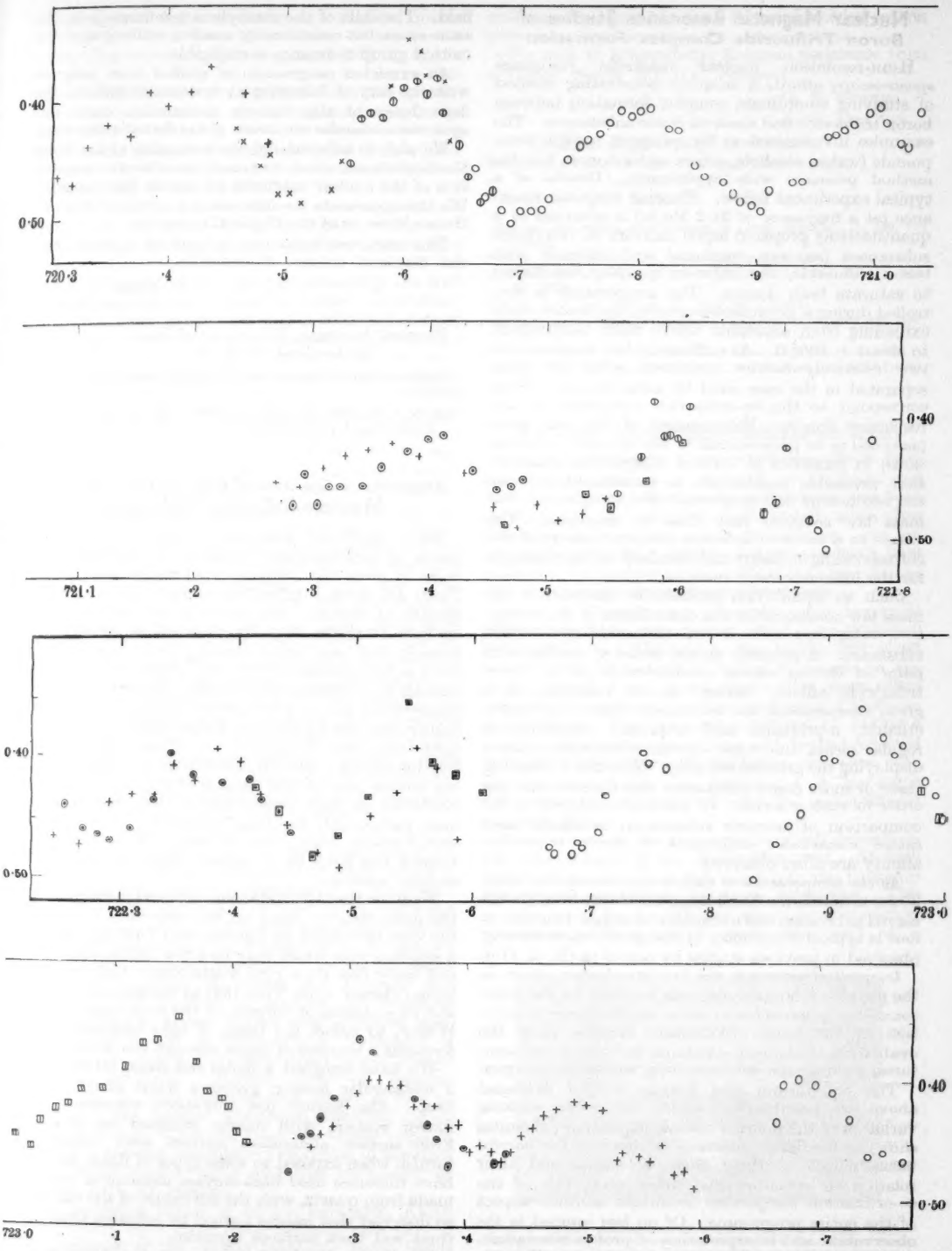

Fig. 1. Light curves of 12 Lacertae. +, Simeis; ⊙, Abastumani; ⊡, Bialkov; ○, Lick; □□, Tokyo; ⊕, Yale; ×, Utrecht.
Abscissa: Julian days minus 2,435,000; ordinate: magnitude difference, 12 Lac.–10 Lac.

Nuclear Magnetic Resonance Studies of Boron Trifluoride Complex Formation

High-resolution nuclear magnetic resonance spectroscopy affords a uniquely penetrating method of studying co-ordinate complex formation between boron trifluoride and electron donor substances. The examples investigated so far comprise oxygen compounds (water, alcohols, ethers and ketones), but the method promises wide application. Details of a typical experiment follow. Fluorine magnetic resonance (at a frequency of 34·2 Mc./s.) is observed in a quantitatively prepared liquid mixture of two donor substances (as, say, methanol and ethanol) with boron trifluoride, the latter in quantity insufficient to saturate both donors. The temperature is controlled during a given measurement, the usable range extending from somewhat above room temperature to about − 100° C. At sufficiently low temperatures two relatively narrow resonance peaks are seen, separated in the case cited by some 70 c./s. These correspond to the co-ordination complexes of the respective donors. Measurement of the peak areas (assumed to be proportional to the volume concentrations) in mixtures of various composition indicates that reversible equilibrium is established between the two donors and their respective complexes. The mass law constant may thus be measured. The values at a series of different temperatures yield the corresponding enthalpy and standard entropy changes for the interconversion reaction.

Such an equilibrium constant is the ratio of the mass law constants for the dissociation of the respective complexes into boron trifluoride and donor substance. A properly chosen series of studies with pairs of donors allows establishment of a 'boron trifluoride affinity' series; as an example, at a given temperature the substances water, methanol, ethanol, *n*-propanol and *n*-butanol constitute a regular series, the water – boron trifluoride complex displaying the greatest stability. Mixtures containing three or more donor substances also demonstrate the order in such a series. Of particular interest is the comparison of isomeric substances, in which cases rather remarkable differences in boron trifluoride affinity are often observed.

As the temperature of such a mixture as that cited above is raised, the two fluorine resonance lines are observed to broaden and ultimately to merge. This behaviour is typical of chemical exchange effects, as already observed in previous studies by one of us (R. A. O.)[1].

In qualitative terms, the line broadening occurs as the pseudo-monomolecular rate constant for the interconversion approaches in value the frequency separation of the lines. Systematic studies allow the evaluation of the rate constants at various temperatures, yielding the corresponding activation energies.

The equilibrium and kinetic studies indicated above are possible because of the rather striking variation of the fluorine resonance position ('chemical shift') as the donor substance is altered. The careful measurement of these chemical shifts, and their relation to structure and other properties of the co-ordination complexes, constitute another aspect of the entire programme. Of no less interest is the observation and interpretation of proton resonances. As an example, the formation of the boron trifluoride complex of ethanol results in a marked displacement (more than 100 c./s. as compared with pure ethanol) of the hydroxyl proton resonance toward lower magnetic field. The shift of the methylene resonance is in the same sense, but considerably smaller, while that of the methyl group resonance is negligible.

An extended programme of studies is in progress with the aim of following in systematic fashion the dependence of the various measurable quantities upon the molecular structure of the donor substances.

We wish to acknowledge the assistance of the Swiss National Fund, which has made possible the acquisition of the nuclear magnetic resonance spectrometer. We also appreciate the interest and advice of Prof. P. Huber, director of the Physical Institute.

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Absorption Spectra of Flat Flames using a Multiple-Reflexion Technique

Many previous attempts to detect absorption bands of intermediate oxidation or pyrolysis products in premixed (Bunsen-type) flames have failed. There are several difficulties in studying absorption spectra of flames; the reaction zone where intermediate products may be expected is usually extremely thin and often curved; it is necessary to have a background source the brightness of which exceeds that corresponding to the effective excitation temperature in the flame (which may sometimes be higher than the equilibrium flame temperature); the light beam may be thrown out of the flame by refraction effects; and the concentration of the absorbing species may be low because of their instability or reactivity at high temperatures, thus necessitating long path-length for their detection. To study a thin reaction zone, even if flat, it is necessary to restrict the light to a narrow beam of very small angular aperture.

We have recently made some progress in overcoming the difficulties by using (*a*) flat near-limit flames, of the type developed by Egerton and Powling[1], having a reaction zone which may be a few millimetres thick and fairly flat, (*b*) a very bright xenon high-pressure lamp ('Osram' type *XBO*.162) as background source, and (*c*) a system of mirrors, of the type employed by White[2], to reflect the beam of light backwards and forwards a number of times through the flame gases.

We have designed a metal flat-flame burner with a rectangular matrix, giving a flame about 8 cm. long. The burner has side-tubes containing the mirror system, with quartz windows for viewing. Front-surface aluminized mirrors were found to tarnish when exposed to some types of flame, and we have therefore used back-surface aluminized mirrors made from quartz, with the curvature of the surfaces so designed that images formed by reflexion from the front and back surfaces coincide.

Gradients of refractive index in the flame gases are low under our experimental conditions, and have not caused appreciable defocusing with less than twenty traverses.

Exposures of usable intensity on a medium quartz spectrograph have been obtained in 30 min., with twenty-four traverses in the region of 2500 A., and in 10 min., with thirty-six traverses in the visible region. With fewer traverses than those just quoted, it is possible to increase the spatial resolution in the flame gases by stopping down the vertical aperture. Good quartz/lithium fluoride achromat lenses have been used for ensuring good focus in the near ultra-violet as well as the visible.

Flames of diethyl ether with air show a weak cool flame below the main blue-flame front, near the rich limit. Under carbon-forming conditions, there is a dark zone between the main blue-flame front and the yellow carbon zone, and the gap separating the cool flame from the main flame is barely discernible; the carbon zone appears for only a relatively narrow range of mixture strengths, disappearing for the richest mixtures. For these ether flames we have found clear, strong absorption bands of formaldehyde (3500–2600 A.) which are strongest in the region between the cool and main flames. Under carbon-forming conditions and with a path-length of nearly 200 cm., benzene absorption bands have been found (λλ 2589, 2528 A.). The absorption bands of formaldehyde have also been detected in flames of acetaldehyde and methanol with air; the latter did not show a discernible cool flame. The hexane/air flame shows the benzene bands much more clearly than the ether flame; also an unidentified band of intensity comparable with the benzene system has been observed at about 2750 A. The bands first occur in the preheating zone well below the main flame front and persist through to the carbon zone. They do not, however, show any marked increase in intensity towards the carbon zone. Some continuous absorption is also observed in the short-wave ultra-violet in the dark space between the main flame front and the carbon zone, but no formaldehyde has been detected. For this work, the hexane was carefully freed from contaminating benzene. A trace of benzene absorption has been found in flames of methane and propane, but has not finally been confirmed.

Formaldehyde has previously been detected by Egerton and Pidgeon[3] in the slow combustion of hydrocarbons, and its occurrence in ether flames is not unexpected. The new observation of benzene is more interesting and could be used as an argument to support a theory of ring closure as a stage in carbon formation, rather than one depending on breakdown of acetylene to carbon. Processes of carbon formation have been discussed by Street and Thomas[4] and Gaydon[5]. The presence of benzene and weakness of formaldehyde in the hexane flame suggest that, in premixed flames of hydrocarbons, formation of pyrolysis products is more rapid than that of partial oxidation products. Recent work[6] on benzene absorption at high temperatures shows a loss of structure; the banded absorption observed by us probably comes, therefore, from the cooler parts of the flame, and the continuous absorption in the dark space of the hexane flame may also be caused, at least in part, by benzene.

For explosion flames of carbon monoxide, Knipe and Gordon[7] have given some evidence that part of the structure of the carbon monoxide flame bands may be due to absorption, possibly by carbon monoxide molecules in the $a^3\Pi$ state. We have looked for both the triplet and third positive systems of carbon monoxide in absorption, using up to thirty traverses through a rich-limit flame of undried carbon monoxide, but have seen no signs of them.

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Low-angle X-ray Observations on Glass

Various low-angle X-ray scattering effects from some glasses have been reported by Hoffman and Statton[1]. Essentially the same experiment has been carried out on similarly heat-treated silica-glass plates using monochromatic X-radiation, and no low-angle diffraction effects of any sort have been observed. A possible explanation of the observations of Hoffman and Statton is considered here.

Lu and Chang[2] also observed some low-angle diffraction effects from glasses, which were explained by Rooksby and Thomas[3] as due to the very short wave-lengths of the white radiation present in the nickel-filtered X-ray beam used. The same effect appears to be operative in the experiments of Hoffman and Statton. This has been confirmed by taking a photograph of a silica plate, first with crystal-reflected monochromatic copper K_α radiation, and then with nickel-filtered copper K_α radiation. A low-angle diffraction ring is observed with the nickel-filtered radiation (Fig. 1).

The position of the low-angle ring will depend on the peak voltage of the X-ray tube used. At high tube-voltages, the band will move into the backstop and appear as diffuse low-angle scattering. This would account for the different behaviour of quenched and annealed samples of silica glass and of a

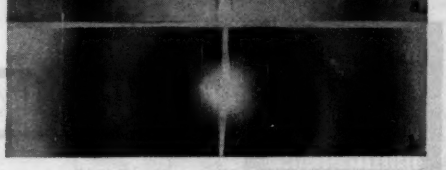

Fig. 1. X-ray photographs of a silica plate, 0·18 mm. thick, using (*a*) monochromatic copper $K\alpha$ radiation, by reflexion from a lithium fluoride crystal. The photograph was taken in vacuum, in a focusing camera, 7 cm. in diameter; (*b*) nickel-filtered radiation. Photograph taken in air, on a flat plate, 7·5 cm. from specimen. The peak voltage of the X-ray tube was 35 kV., and the nickel foil was 0·001 in. thick. In the case of the nickel-filtered radiation, a low wave-length component of the white radiation remains, which produces the low-angle inner ring

soda–magnesium oxide–silica glass reported by Hoffman and Statton. Their observations on a glass fibre are affected by the different absorption effects perpendicular and parallel to the axis of the glass fibre. The sharpness of the low-angle ring will depend on the thickness of the nickel filter, the thickness of the specimen, type of film emulsion, condition and type of X-ray tube, conditions of collimation of the X-ray beam, and the absorption edges of silver (0·48 A.) and bromine (0·92 A.). Evidently, Hoffman and Statton employed very delicate conditions, which produced a remarkably sharp low-angle band.

I am indebted to Dr. E. A. Calnan and Mr. H. P. Rooksby, with whom this phenomenon was discussed, to Prof. H. J. Emeléus for interest in the work, and to the Owens-Illinois Glass Co. for supporting the work.

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Guarded-Field Thimble Ionization Chambers

In a previous communication[1] a new guarded-field principle as applied to ionization chambers was outlined, together with its attendant advantages. A thimble chamber employing the new system comprises a cylindrical conducting wall, subdivided into a number of annular sections of equal width ω situated between two end-sections of width ½ω, as shown in Fig. 1,*a*. These wall-sections are all insulated from one another, either by narrow surface grooves in the case of a wall of insulating material having a conductive coating, or by thin insulating washers in the case of a wall of conducting material. The two half-sections at either end are in electrical continuity with the adjacent (plane) end-surfaces of the cylindrical chamber cavity. If equal potential differences are maintained across each of the insulating gaps in the cylindrical wall, the associated electrostatic field distribution is somewhat as shown in Fig. 1,*a*. (An alternative mode of subdivision of the wall into sections of equal width throughout is also possible, but involves the use of unequal voltage steps.)

For a given chamber-cavity radius R, and annular wall-section width ω, there will be a corresponding cylindrical volume, coaxial with the chamber cavity

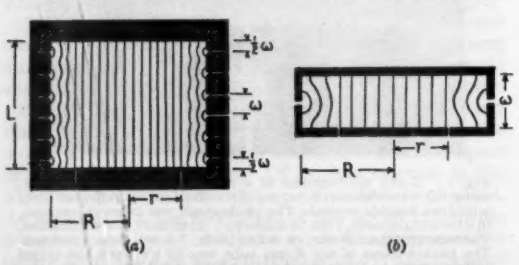

Fig. 1. Two types of guarded-field chamber: (*a*) multi-section; (*b*) single-section

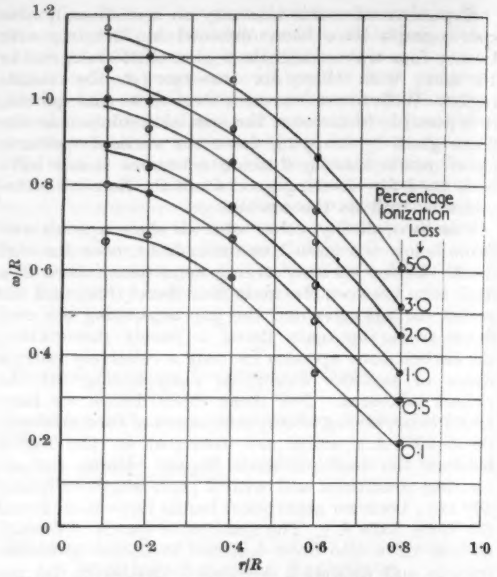

Fig. 2. Basic design curves for guarded-field thimble chambers, enabling the relationship between r, R and ω to be determined for any chosen level of ionization loss

and of radius r, throughout which the field lines will be sensibly straight. Thus a circular collecting-electrode of radius r can be employed, comprising a part of one of the plane ends of the chamber cavity, but separated by a narrow gap (of the order of one- or two-thousandths of an inch in practice) from the guard surface surrounding it. Clearly, the volume from which ions are collected by such an electrode is given accurately (and simply) by $\pi r^2 L$, where L is the length of the chamber cavity. Thus, for the practical purpose of chamber design, it is required to know the relation between r,R and ω which will guarantee adequate linearity of the field lines terminating on the collecting electrode.

We have investigated this relationship ionometrically in a series of precision experiments in which the ionization losses associated with a range of values of ω (for given r and R values) were studied, the gaps between the wall sections being maintained at 0·1ω throughout. (For these experiments a chamber 3 cm. in diameter was used, in conjunction with a telecobalt unit for the production of the ionization.) The results are given in Fig. 2, in which ω/R is plotted against r/R, with ionization loss as parameter. The range of values of r/R covered by the experiments was 0·1–0·8 inclusive, but the extrapolation of at any rate the lower loss lines towards the point $\omega/R = 0$, at $r/R = 1{\cdot}0$, seems justifiable.

As an example of the use of these curves we may suppose that it is required to construct a chamber of cavity radius 1·5 cm., with a collecting-electrode radius of 1·0 cm., and that ionization losses are not to exceed 0·1 per cent. From the relevant curve in Fig. 2 (since $r/R = 0{\cdot}67$) we obtain $\omega/R = 0{\cdot}31$, whence, for $R = 1{\cdot}5$ cm., $\omega = 0{\cdot}465$ cm. Any convenient value of ω not exceeding 0·465 cm. may obviously be used.

This information can be utilized for the construction either of a multi-section chamber (Fig. 1,*a*) or a single-section chamber (Fig. 1,*b*). The latter might

correspond to a so-called 'extrapolation-type' chamber, in which the earthed guard-surface surrounding the collecting electrode, and the upper (plane) surface of the chamber cavity (to which the polarizing voltage is applied), are each carried over by means of a conductive coating on to the cylindrical wall, being separated midway by a narrow gap. The data given in Fig. 2 will obviously enable such a chamber to be constructed with the maximum possible diameter of collecting electrode for given chamber dimensions.

A full account of this work and its application to radiation dosimetry will be published elsewhere.

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Effect of Tube Diameter on the Pressures in Gaseous Detonation Waves

It has been shown by Kistiakowsky *et al.*[1,2] that the velocities of plane detonation waves in the steady state in gaseous mixtures contained in straight tubes are influenced by the energy losses to the walls of the tube. For tubes the diameters of which are less than 10 cm., the velocities are found to decrease with decreasing diameter; this effect is attributed to the formation at the wall of the tube of the rarefaction wave, which travels inwards with acoustic velocity, thereby causing a lowering of temperature and the rate of chemical reaction. Such a rarefaction can be produced by two mechanisms, namely, cooling of the gas in contact with the wall and frictional drag at the wall. The individual effects are indistinguishable experimentally.

It is of some interest to investigate the influence of tube diameter on the (pressure, time) relationships of the waves, since the effect in this case is likely to be more pronounced than in the case of velocity. A series of measurements, of both static and reflexion pressures, were carried out in three detonation tubes of diameters 10, 3·8 and 1·6 cm. Each tube was 10 ft. in length and detonation was initiated at one end by means of a copper acetylide matchhead. Specially designed pressure bar-gauges were employed to record the pressures. Only the results obtained for the mixture $2H_2 + O_2$ will be described here. Typical (pressure, time) curves for the static condition are shown in Fig. 1.

In the static pressure records obtained in the 10 and 3·8 cm. tubes the initial peak lying in the region 0–20 μsec. can be attributed to a combination of dispersion effects in the bar of the gauge[3] and to excitation by the von Neumann pressure 'spike'[4] even though the gauge is incapable of resolving the extremely short-duration reaction zone. The Chapman–Jouguet pressures have therefore been taken to be the average values between approximately 20 and 80 μsec. In both these tubes, for this particular mixture, the measured Chapman–Jouguet pressures agree well with the theoretical value of 18·05 atmospheres. A completely different (pressure, time) relationship, however, is observed in the 1·6-cm. tube. Here the pressure, which has a peak value of 24·6

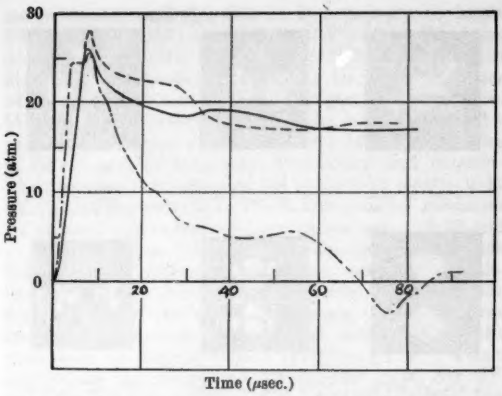

Fig. 1. Static (pressure, time) curves for plane detonation waves in a stoichiometric $2H_2 + O_2$ mixture in tubes of various diameters; 10 cm. diam., ——, 3·8 cm. diam. – – – –, 1·6 cm. diam. — – — –

atm., drops rapidly after about 8 μsec. and thereafter oscillates about a low value. As would be expected, the reflexion pressure records do not exhibit such marked differences.

The original records show oscillations which have been smoothed out in Fig. 1 in order to show the general trend more clearly; the periods of these oscillations agree closely with the times of traverse of a sound wave in the hot gases behind the detonation front, across the respective tube diameter. These times in the case of $2H_2 + O_2$ for the 10, 3·8 and 1·6 cm. tubes are 63, 24 and 10 μsec. respectively. Confirmation of this fact was obtained in mixtures with different acoustic velocities, and it lends support to the hypothesis that energy is abstracted from the detonation wave through the formation of rarefaction waves at the wall of the tube.

We wish to thank Prof. R. M. Davies for his encouragement and interest in this work, and one of us (D. H. E.) would like to acknowledge his indebtedness to the University of Wales for an I.C.I. Fellowship, and the other (G. T. W.) to the Department of Scientific and Industrial Research for a maintenance allowance.

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Adsorption of Water on Tungsten

The adsorption of water on tungsten and its subsequent desorption have been studied using the technique of field emission microscopy[1]. The field emission patterns obtained from a tungsten cathode at a pressure of water equal to 4×10^{-9} mm. are shown in Figs. 1 and 2. The times given are those for which the tip was exposed to water vapour after a 2-min. flash at 2,500° K. These patterns are quite different from those obtained during the adsorption of

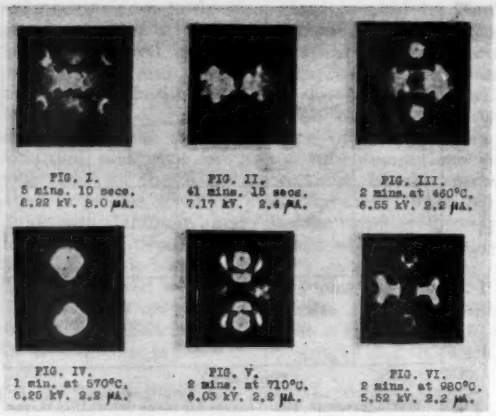


FIG. I. 5 mins. 10 secs. 6.22 kV. 8.0 μA.

FIG. II. 41 mins. 15 secs. 7.17 kV. 2.4 μA.

FIG. III. 2 mins. at 460°C. 6.55 kV. 2.2 μA.

FIG. IV. 1 min. at 570°C. 6.25 kV. 2.2 μA.

FIG. V. 2 mins. at 710°C. 6.03 kV. 2.2 μA.

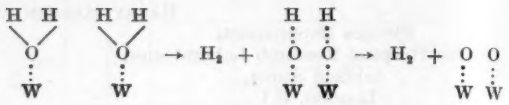
FIG. VI. 2 mins. at 980°C. 5.52 kV. 2.2 μA.

either hydrogen or oxygen on tungsten[2]. In Fig. 1, the central 011 plane appears to be strongly emitting, in contrast to oxygen adsorption when it remains dark for at least 20 min. at this pressure. Closer inspection reveals that the strongest emission is actually from the region immediately surrounding this plane. After prolonged exposure to water (Fig. 2), the 012 region is very dark and the main emission is from the 111 region. The abrupt change in work function in crossing a line drawn diagonally from the central 011 plane and just missing the 112 plane is most remarkable.

The tip was then heated, usually for 2 min. but sometimes for 1 min., at increasing temperatures about 100–150° apart. Some of the characteristic patterns obtained are shown in Figs. 3–6. At first the pattern changes but little, apart from a general brightening in the 001 region which commences at about 200° C. and indicates the desorption of water. The evolution of gas is confirmed by increased ion gauge pressure-readings, excess gas being pumped away so that a steady pressure of 4×10^{-9} mm. was maintained. This process is continued on raising the temperature to 460° C., which results (Fig. 3) in bright emission from the 001 region which is accentuated by a very dark surrounding ring. The remainder of the emission is largely from the 111 region. A very marked change in pattern occurs between 460 and 570° C., the pattern obtained after 1 min. at 570° C. (Fig. 4) strongly resembling the early stages of water adsorption. The strongly emitting 001 region is reminiscent of slight oxygen contamination, but the 111 planes are darker than is the case for oxygen adsorption.

Further remarkable changes are apparent after heating the tip for 2 min. at 710° C. The darkened 111 plane is now light again while higher index planes in that region remain dark (Fig. 5). The dark cross, so characteristic of oxygen adsorption, formed by the diagonals joining the 112 planes, is now evident together with bright patches due to emission from the 012 planes. The 001 region is, however, still very different from its appearance under an oxygen film. After 2 min. at 980° C., the 111 plane and the bridges (233, 122, 133) joining it to the 011-type planes present a 'built-up' appearance. This is a characteristic feature of an oxygen-contaminated tip after heat treatment and is due to the migration of tungsten under an oxygen layer. The 001 planes are, however, still dark. This latter feature is finally removed at 1,200° C., resulting in a pattern indistinguishable from those observed during the desorption of oxygen.

To summarize: desorption of water occurs between 200 and 460° C.; between 460 and 570° C. abrupt changes occur in the field emission patterns, which, as the temperature is further increased, show an increasing resemblance to those of oxygen on tungsten. The desorbed water probably comes from the second layer. When the first layer is laid bare, decomposition of water occurs, possibly by the mechanism:



This results in a layer of adsorbed oxygen. The reaction appears to take place first on the 111 planes at about 700° C., but a completely water-free oxygenated tip is not obtained below 1,200° C. Fuller details of this work will be published elsewhere.

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Excess Volumes in Binary Liquid Mixtures of Simple Molecules

Recent statistical theories of liquid mixtures have made it possible to calculate the excess thermodynamic functions of binary mixtures from the parameters characterizing the intermolecular potential-energy curves for the two pairs of like molecules. For small molecules, between which only dispersion forces are supposed to operate, these parameters may conveniently be taken to be ε_{11}, the minimum value of the potential energy, and r_{11}, the molecular separation corresponding to this minimum (for a pair of like molecules of species 1). The theories are of two types. Those of the first type use a definite model for the liquid, and enable the excess functions to be calculated from the appropriate ε and r values alone. This applies to the treatment of Prigogine and Mathot[1] (and its extension by Prigogine and Bellemans[2]) and to that of Salsburg and Kirkwood[3]. In treatments of the second type[4,5], based on the theory of corresponding states, the excess functions are expressed in terms of (*a*) the ratios $\varepsilon_{11}/\varepsilon_{22}$ and r_{11}/r_{22} and (*b*) the macroscopic properties of one of the two pure components, chosen as reference substance. Thus, the excess volume, V^E, depends on the molar volume of the reference liquid and the temperature variation of this volume.

These theories, which should be tested on systems composed of small, symmetrical, non-polar molecules, predict that V^E can either be positive or negative. Qualitatively, differences in ε tend to give rise to a

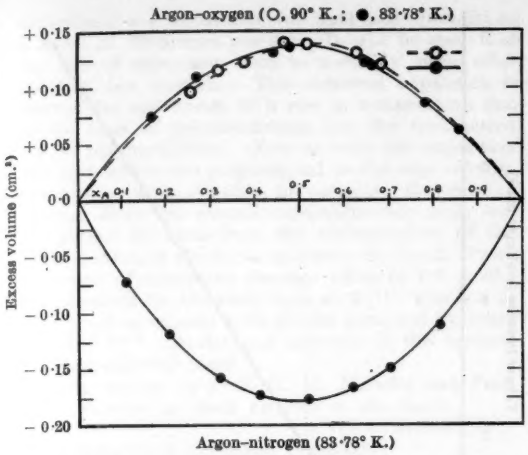

Fig. 1. Plot of the volume change on mixing V^E, in ml./mole, against x_A, the mole fraction of argon, in the systems argon–oxygen and argon–nitrogen

contraction on mixing, and differences in r to an expansion.

We have measured the excess volumes for the systems (*a*) argon–nitrogen at the triple-point of argon (83·78° K.), (*b*) argon–oxygen at 83·78° and at 90·00° K. The method used was essentially the same as that first applied to the system carbon monoxide–methane[6], but its precision was considerably improved, principally by using a rather larger sample of liquid (~ 2·3 ml.) and by increasing the accuracy of the pressure measurements on which the determination of the amount of each component in the pycnometer depends. If $V_{obs.}$ is the molar volume of a mixture in which x_1 and x_2 are respectively the mole fractions of the components 1 and 2, and if V^0_1 and V^0_2 are the molar volumes of the two pure components, then $V^E = V_{obs.} - x_1V^0_1 - x_2V^0_2$. The experimental values of V^E in ml./mole are plotted in Fig. 1. They may be represented by the equation $V^E/x_1x_2 = A + B(2x_1 - 1)$, where subscript 1 refers throughout to argon, and where the parameters A and B have the following values: for argon/nitrogen at 83·78° K., $A = -0·7191 \pm 0·0022$, $B = 0·0025 \pm 0·$[illegible], for argon/oxygen at 83·78° K., $A = 0·5442 \pm 0·0028$, $B = -0·0011 \pm 0·008$; for argon/oxygen at 90° K., $A = 0·5508 \pm 0·0026$, $B = 0·044 \pm 0·009$. The method used necessarily yields values for the molar volumes of the pure liquids of high relative precision. These values in ml./mole are as follows: for nitrogen, 36·091 at 83·78° K.; for argon, 28·193 at 83·78° K. and 28·967 at 90° K.; for oxygen, 27·300 at 83·78° K. and 28·023 at 90° K.

We shall now compare experiment and theory for equimolar mixtures ($x_1 = x_2 = 0·5$). The necessary values of ε and r can be obtained from second virial coefficient data, from gas viscosity data, or by using relations between ε and r and the critical constants[7]. For the system argon–nitrogen, V^E is negative, being − 0·180 ml./mole at 83·78° K. Theories of the first type, however, predict a positive V^E, regardless of the source of the ε and r values. This is due essentially to the difference of ~ 0·3 A. between the r values for argon and nitrogen. To test the second type of theory, one of the two substances is chosen as reference, and for this it is necessary to know V^0, $V' (= dV^0/dT)$ and $V'' (= d^2V^0/dT^2)$. We have combined our own values of V^0 with the data of Mathias, Crommelin and Onnes to give estimates of V' and V'' for argon, nitrogen, and oxygen. With argon as reference substance and with ε and r values taken from virial coefficient data, the theories of Scott[5] and of Prigogine, Bellemans and Englert-Chwoles[4] predict values of V^E of + 0·17 and + 0·12 ml./mole respectively. With nitrogen as reference substance, the corresponding values are −0·29 and − 0·32 ml./mole. Besides the change in sign with the choice of reference substance, another unsatisfactory feature here is the uncertainty about the convergence of the series expansions on which these treatments depend. Thus, our estimates of the quantities in the expression $(\frac{1}{2}TV' + \frac{1}{6}T^2V'')$, which appears in the equation of Prigogine *et al.* for V^E, are for argon $\frac{1}{2}TV' = 5·3$, $\frac{1}{6}T^2V'' = 1·7$; but for nitrogen, the corresponding values are 8·5 and 17.

For an equimolar mixture in the argon–oxygen system, $V^E = + 0·136$ ml./mole. The critical constants of argon and oxygen only differ slightly, so it is not surprising that with values of ε and r derived from these constants the values of V^E calculated from the theories we are considering are numerically always much too small ($< 0·005$ ml./mole). Scott's treatment, in which the ε values are derived from vaporization energies and the r values from the molar volumes of the liquids at the temperature in question, also predicts a small V^E ($< 0·01$ ml./mole). If, however, we take the r values from second virial coefficient data and choose those quoted by Hirschfelder *et al.*[7] to make the difference between them as large as possible (namely, $r = 3·838$ A. for argon and 4·02 A. for oxygen), the theories predict an expansion of the right order of magnitude. Thus, Salsburg and Kirkwood's equations[3] give $V^E = 0·21$, and those of Prigogine, Bellemans and Englert-Chwoles, selecting argon as the reference substance, give 0·12 ml./mole. Nevertheless, an appreciable difference in r for the two sets of molecular pairs, in view of the near-equality of the critical constants, suggests that oxygen is not conforming closely to the principle of corresponding states in the simple form valid for spherical molecules. This is indeed implied by the figures of Table 4, 1–2, p. 245, of Hirschfelder's book[7]. In the argon–oxygen system, a contributory factor to attraction between oxygen molecules is their paramagnetism, and consequently an assumption made in all theoretical treatments we have considered, namely, that ε_{12} is the geometric mean of ε_{11} and ε_{22}, may be a less sound approximation for this system than for others. If an equilibrium governed by an ideal mass-action law is assumed to exist between O_2 and O_4 molecules, any contribution to V^E arising from the effect on this equilibrium of dilution with argon should in principle be an unsymmetrical function of mole fraction. In fact, V^E is an almost perfectly symmetrical function of composition at the lower temperature, though an increase in temperature appears to make it slightly less so.

It is hoped to measure other excess properties of these two systems, but it is clear that for testing and comparing various statistical theories it is just as important to have the best available information on intermolecular energy parameters and on the physical properties of the pure substances concerned

as it is to obtain new experimental information about the excess properties of suitably selected systems.

We thank the British Oxygen Company for the award of a fellowship to one of us (R. A. H. P.).

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A Dilatometric Method of following the Non-stationary State of Polymerization Reactions

In recent years, several non-stationary state methods[1–5] have been developed for the measurement of kinetic life-times and hence the velocity coefficients for the propagation and termination steps in polymerization reactions. These methods, with the exception of that of Burnett[1], depend upon the system remaining virtually adiabatic for periods of at least 10 sec. following the commencement of irradiation; this is due to the very slow conduction of heat through the walls of the reaction vessels. Burnett's results, which were interpreted on the basis of the system remaining isothermal during the reaction, can alternatively be explained[6] if non-isothermal conditions prevail during the reaction. This, however, invalidates the method as a means of measuring non-stationary states. The method reported here, like that of Burnett[1], involves the measurement of change of volume immediately following the beginning of irradiation, but differs in that the non-stationary state period is measured from the volume expansion–time curve instead of the contraction–time curve.

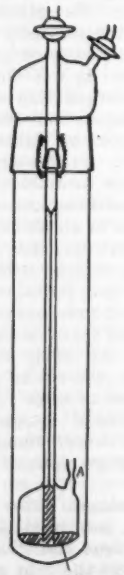

Fig. 1. Dilatometer and vacuum jacket. Constriction at *A* is sealed when dilatometer has been filled with monomer

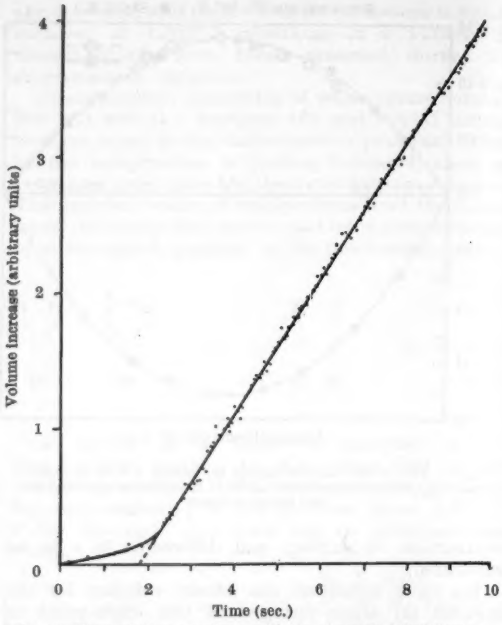

Fig. 2. The variation of volume with time immediately following the commencement of irradiation of vinyl acetate photosensitized with 1.1′ azo-*bis*-*cyclo*hexane carbonitrile at 25° C.

Preliminary experiments on the polymerization of vinyl acetate photo-sensitized with 1.1′ azo-*bis*-*cyclo*-hexane carbonitrile indicated that the reaction was adiabatic for approximately 8 sec. when a dilatometer of about 50 ml. capacity was used, the dilatometer being immersed in a thermostatically controlled water-bath. This period could be increased five-fold or more by placing the dilatometer inside a glass jacket which was afterwards evacuated. The final arrangement used, shown in Fig. 1, consists of a dilatometer bulb of about 20 ml. capacity attached to constant bore (Veridia) capillary tubing of 0·4 mm. diameter. The height of the meniscus in the capillary tubing can be adjusted by the addition or removal of mercury.

The usual method of following the movement of the meniscus with a cathetometer could not be employed as the system remained adiabatic for only about 30 sec. The movement, however, could be photographed through the telescope of a cathetometer using a ciné-camera. Alternatively, the cross wire in the telescope of a cathetometer could be replaced by a piece of processed film on which is printed a series of equidistant parallel lines. As the meniscus crosses each of these lines in turn, the observer could record the time by depressing a button switch which applied an electromotive force to the pen-recording voltmeter. Either method was satisfactory, but the latter method proved to be much less time-consuming.

An expansion–time curve for the polymerization of vinyl acetate is shown in Fig. 2. In this particular

experiment a ciné-camera was used and operated at a speed of 16 frames per sec. It will be seen that the rate of expansion rises to a steady value after the first few seconds. The observed expansion is clearly the net result of a rise in temperature due to the heat of polymerization less the contraction due to polymerization. Now as both the expansion and contraction are proportional to the rate of polymerization, it is possible to calculate the rate of reaction from the overall expansion–time plot, and the kinetic life-time from the extrapolation of the linear portion of the curve as shown in Fig. 2. From a number of results an average value of $2 \cdot 9 \times 10^{-5}$ was obtained for the ratio k_p/k_t at 25° C. which is in quite good agreement with results obtained by other methods[3,4,7–9]. A detailed account of the method will be published later.

I am grateful to Prof. H. W. Melville and Prof. P. D. Ritchie for their interest in the work.

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Relationship between the Concentration of Anionic Surface-active Agents and the Electrophoretic Mobility and Viability of *Aerobacter aerogenes*

As part of a detailed study of the electrical properties of *Aerobacter aerogenes*, it was considered that useful information on the action of phenol could be obtained by following changes of the electrophoretic mobility of the organism after treatment with this reagent.

Cells of this organism, grown in synthetic medium[1], were harvested early in the logarithmic growth phase, washed twice with phosphate buffer solution (ionic strength = 0·013, *p*H = 7·00) and then suspended in buffer solutions containing various concentrations of phenol. The suspensions (3×10^8 organisms per ml.) were aerated for thirty minutes at 40° C.; the organisms were then washed and suspended in phosphate buffer solution and the mobility distributions determined[1]. The histograms (Fig. 1) show the distributions of mobility after treatment; these are reproducible after prolonged keeping of the final suspension. At low concentrations, the mobility (homogeneous) is less than that of the control, but at higher concentrations than those used previously[2] higher mobility values (negative) were obtained, first as a heterogeneous and finally as a homogeneous population.

The initial decrease of mobility may be attributed to the bonding of phenoxy ions with receptor sites throughout the depth of the cell wall, resulting in a partial neutralization of negative charges (cf. ref. 2). However, only changes in those layers which contribute to the ζ-potential (possibly only the upper layers) will be observed by this technique. The subsequent increase in mobility, which cannot be reconciled with this theory, is believed to be due to the adsorption of a second layer of ions by van der Waals forces, with their polar groups oriented outwards. A study of the *p*H/mobility relationship for the treated cells, and also the similar behaviour on treatment with sodium dodecyl sulphate lend support to such a theory. It has not been possible to confirm this by analysis, since the chemical methods of determining the very small amounts of phenol adsorbed are not sufficiently sensitive; it is hoped, however, to pursue this further, using phenol labelled with carbon-14. A similar theory has already been advanced to explain certain anomalous characteristics of complexes formed with sodium dodecyl sulphate and gelatin[3] and with hæmoglobin[4].

On this hypothesis it is most likely that the first layer of ions is nearly complete before the second layer starts to form, with the resulting increase of mobility. It was found that the concentration of

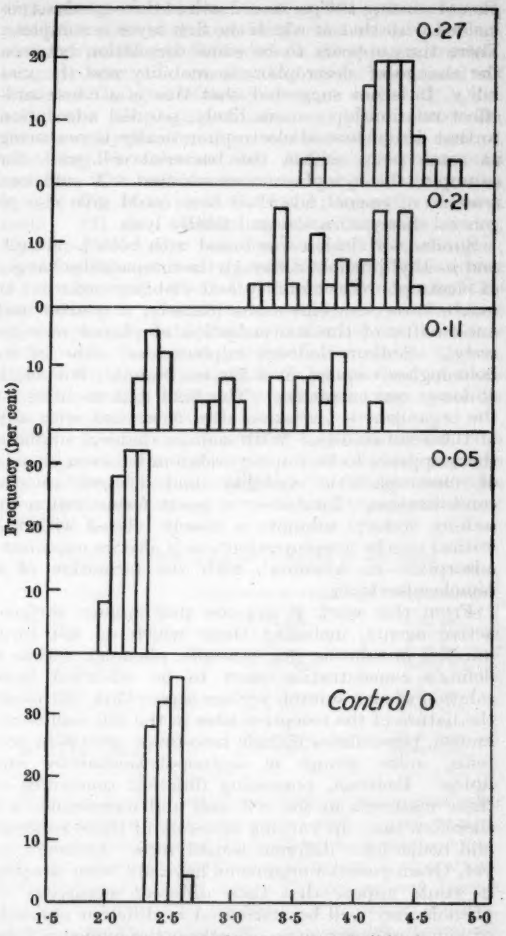

Fig. 1. Histograms showing the distributions of electrophoretic mobilities of *Aerobacter aerogenes* in buffer solution, after treatment with phenol. (Numbers refer to molarity of phenol used for treatment)

phenol causing 100 per cent death of the organisms coincided with that at which the first layer is complete. There thus appears to be some correlation between the change of electrophoretic mobility and the viability. It is not suggested that this is a cause-and-effect relationship; more likely, parallel adsorption to that demonstrated electrophoretically is occurring at some point within the bacterial cell wall, for example, the cytoplasmic membrane[5]. A sufficient amount of phenol adsorbed here could give rise to general disorganization and finally lysis.

Similar correlation was found with both *p*-methyl- and *p*-ethyl-phenols, although the comparable changes of electrophoretic mobility and viability occurred at much lower concentrations (namely, a quarter and one-twelfth of the concentration of phenol respectively). Sodium dodecyl sulphate and some of its homologues respond in a similar manner, but again at lower concentrations. The final high mobility of the organisms is the same after treatment with any of these substances. With sodium dodecyl sulphate there appears to be some correlation between change of electrophoretic mobility and critical micelle concentration. Inhibition of yeast fermentation by sodium dodecyl sulphate is closely related with the critical micelle concentration[6], as is also its maximum adsorption on alumina[7], with the formation of a bimolecular layer.

From this work it appears that anionic surface-active agents, including those which do not form micelles in solution (for example, phenols), will at a definite concentration start to be adsorbed from solution when a suitable surface is provided. Although the nature of the receptive sites in the cell wall is not known, possibilities include keto-imide groups in proteins, imino groups in aminopolysaccharides and lipids. Bacteria, possessing different quantities of these materials in the cell wall and membrane, will therefore take up varying amounts of these reagents and hence have different sensitivities. Although, as yet, Gram-positive organisms have not been studied, it would appear that their different sensitivity to phenols may well be attributed to different amounts of anion receptor sites. Further, the evidence from the homologous series of phenols studied gives a better understanding of the phenol coefficients, each additional CH_2 group lowering the concentration at which adsorption on suitable sites can occur.

Further work is in progress on the confirmation of the double-layer theory. It is hoped to present a more detailed account of this work later, together with a full discussion of the significance of the histograms.

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A Simple Device for forming Solution Concentration-gradients

The following device for producing nearly linear gradients of concentration can easily be assembled from materials at hand in most laboratories. This design solves the problems arising in such devices from unequal densities of the stock solutions, and has the further advantage of economical operation.

The device, shown schematically in Fig. 1, comprises two identical conical flasks, one upright and one inverted, which feed by gravity to a mixing chamber *M* of small volume. In general, mechanical stirring (magnetic coupling) is desirable in *M*, although in some cases flow through a pebble-bed provides adequate mixing.

The composition of the effluent from *M* is shown in the upper curve of Fig. 2 (calculated on the principle of Ling and Bock[1]). In practice only a truncated conical section of the flasks can be used, so a gradient is begun at $H = 0{\cdot}3$ and ended at $H = 0{\cdot}7$. Between these limits a nearly-linear S-shaped gradient is generated. Fig. 2 shows the effect of changing the height of one flask relative to the other. The lower curve is obtained when the bottom of cone *B* is raised from $H = 1{\cdot}0$ to $H = 0{\cdot}9$. Thus a small misalignment has a slight effect on the linearity of the gradient, but a considerable effect on its slope. When such variations in successive gradients are undesirable, flasks *A* and *B* should be fixed in position and re-filled through their delivery tubes.

A number of devices for producing gradients have been described[1,2], and although the present one embodies no new principle, it possesses two novel features.

First, if *M* is chosen to have a small volume relative to *A* and *B*, there will be negligible holdup in *M* at any fraction of the total volume delivered. Recovery of unused solutions from *A* and *B* can be essentially complete, in contrast to the situation found in devices with a mixing-chamber of large volume. When expensive solvents are employed, the economy afforded by the present device may be significant.

The second point relates to differences in density between the solutions in *A* and *B*. If these differences are large, there will be considerable deviation from the idealized gradients of Fig. 2. This can be over-

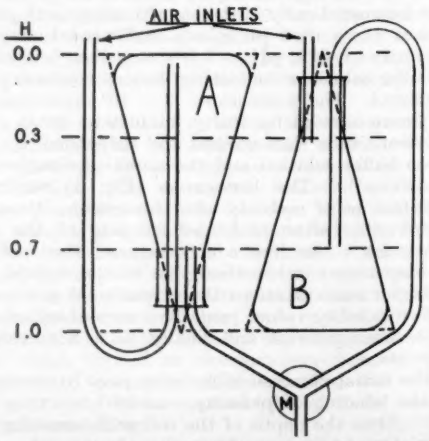

Fig. 1. Apparatus for producing linear gradients of concentration; cones *A* and *B* are both of height $H = 1{\cdot}00$

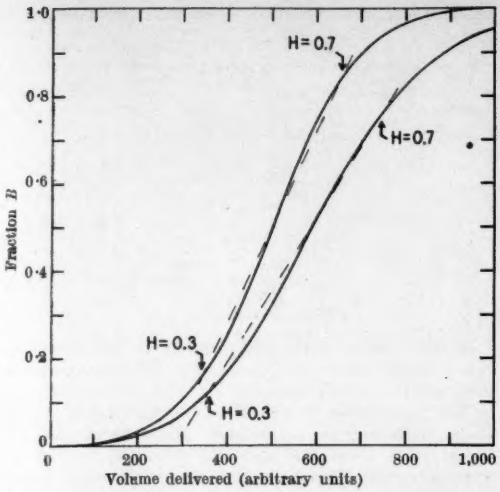

Fig. 2. Gradients generated by flow from cones paired as in Fig. 1. Volume of cone A = volume of cone B = 500 units. Upper curve, cones at same height; lower curve, at different heights

come by the application of an external air pressure P from a manostatted reservoir to the air inlets of both A and B. Then $P+h_{AM}\,d_A=P+h_{BM}d_B$, where h_{AM} is the height between the liquid levels in A and M, d_A is the density of the liquid in A, etc. It is seen that the inequality between h_{AM} and h_{BM} can be made negligible by minimizing the initial values of these quantities and by increasing P (in most cases P can be less than 1/3 atm.). On the application of an external pressure, the flow-rate will of course increase, and it may become necessary to use a flow-resistance element[3] in the effluent tube from M. This solution to the problem of inequalities in density will apply to many devices for producing gradients.

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Effect of Prolonged Thyroid Administration on Aged Male Rats

TISSUES from nineteen aged unaltered male Holtzman strain rats (average body-weight 374·4 gm.) which had been administered orally 0·18 mgm. of 'Proloid' daily (Warner-Chilcott purified thyroid extract) from the age of 14 months to death at 24 months were compared anatomically with those of ten control animals (average body-weight 352·7 gm.) to note any gross or histological anatomical variations induced by the drug. The tissues were fixed immediately following death in buffered 10 per cent formalin and processed routinely by the paraffin method. The tissues examined were testis (including epididymis), kidney, liver, pancreas, buccal gland, seminal vesicle, aorta (both thoracic and abdominal), superior and inferior vena cava, heart, spleen, pituitary, adrenal, prostate and thyroid glands, costal cartilage with surrounding skeletal muscle, diaphragm, trachea, lung, levator ani muscle, abdominal skin and all levels of the gastrointestinal tract including upper and lower œsophagus, fundic and pyloric stomach, duodenum, jejunum, upper and lower ileum, cæcum, ascending, transverse and descending colon and rectum. The sections were stained for examination by the following methods[1-3]: (1) hæmotoxylin and eosin; (2) the Goldner connective tissue stain; (3) the McMannus periodic acid–Schiff technique; (4) the catalysed lead tetraacetate–Schiff technique; (5) the Rinehart–Abu'l–Haj modification of the Hale dialysed iron procedure for acid polysaccharides; (6) the periodic acid–Foot reticular connective tissue stain; (7) the orcein procedure for elastic tissues. It was felt that these methods, when used in comparison, would adequately disclose any possible histochemical variations from the normal.

Prior to fixation, all organs to be processed were carefully examined for gross pathological changes and certain of them were weighed. Weight averages of experimental and control animal organs are listed in Table 1.

Table 1. AVERAGE ORGAN WEIGHTS AT NECROPSY

Organ	Experimental animals	Control animals
Testis	2·94 gm.	2·92 gm.
Kidney	3·12 gm.	3·18 gm.
Spleen	0·70 gm.	1·32 gm.
Seminal vesicle	0·487 gm.	0·388 gm.
Heart	1·28 gm.	1·24 gm.
Pituitary gland	13·9 mgm.	13·2 mgm.
Suprarenal gland	50·8 mgm.	49·8 mgm.
Prostate gland	372·5 mgm.	330·9 mgm.
Thyroid gland	24·1 mgm.	22·6 mgm.
Levator ani muscle	125·7 mgm.	100·6 mgm.

Grossly, no significant pathological variations were noted between the experimental and control organs, either in appearance or by weight; while microscopically, no consistent significant pathological alterations were discernible other than slight generalized fibrosis and the usual changes associated with sexual senility. Changes in the architecture of vascular structures such as arterial muscular and elastic coats and the cardiac muscle fibres were negligible. Ground-substance changes as shown by the histochemical polysaccharide methods could not be considered significant in either series of tissues. It would appear that anatomically this dosage of thyroid preparation over a prolonged period had no material effect on the microscopic or gross architecture of the organs investigated in comparison with the tissues of control animals of equivalent age.

The basal metabolic rates were determined on all the animals just prior to necropsy. These were assessed on the basis of an average of four 10-min. periods and expressed in terms of litres per square metre per hour (l./sq. m./hr.). There was fair correlation between the runs on different days and the thyroid animals averaged 2·84 l./sq. m./hr., while the average of the control group was 1·519 l./sq. m./hr. Heart-rates were determined just preceding death, with the average of the thyroid-fed animals 431·5 beats per min. and those of the control group 416·0 beats per min.

1 c.c. of water containing 4·8 mc. of iodine-131 was administered intraperitoneally to each rat 36 hr. before death. Scintillator counts taken over the thyroid area 24 hr. later averaged 4,998·9 per min.

for the thyroid-fed animals and 6,431·6 per min. for the control group. Planchet counts performed at necropsy on weighed portions of thyroid glands (corrected for total gland) averaged 36,557·8 counts per 3 min. for the experimental animals as compared with an average of 40,808·1 counts per 3 min. for the control group.

The animals receiving the exogenous thyroid had a statistically significant increase in basal metabolic rates over the control group in spite of the decreased thyroid function of the experimental animals as indicated by iodine-131 uptake studies. It is also of interest that the average heart-rate of the thyroid-fed animals was not significantly higher. Thus, it would seem that when exogenous thyroid has been administered to the aged rat over a prolonged period of time thyroid function is to some extent altered; but this depression is not sufficient to counteract the additional stimulus produced by the thyroid fed to the animal.

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Calorigenic Action of Glucagon

A recent investigation carried out in this laboratory revealed that rats treated with glucagon gained less weight and contained much less fat, protein and water than pair-fed controls. Since the calorie intake of the two groups was identical and the calorie values of the carcasses of the glucagon-treated rats was much lower than that of the controls, the effect of glucagon on the metabolic rate of rats was investigated.

Male Wistar rats were used throughout the investigation. Of the eight animals used for each experiment, four were injected subcutaneously with 1 mgm. of crystalline glucagon (Lilly, Lot No. 258–234–*B*–54–2) suspended in neutral saline. The remaining four rats served as controls and were injected with saline. The oxygen consumption of each animal was determined at an environmental temperature of 28° C., according to the method of Ferguson and Sellers[1] at the intervals shown in Table 1. Four identical experiments were performed in this manner using rats that ate *ad libitum* up to the time of injection. A second group of similar experiments was carried out using rats that had been fasted 24 hr. prior to injection.

It is evident from Table 1 that glucagon induced a rise in the metabolic rate of the fed animals of approximately 35 per cent. The increase in oxygen consumption was maximal 1 hr. after the administration of glucagon and decreased slowly throughout the 7-hr. observation period. It is also evident from Table 1 that this effect of glucagon is only slightly reduced when the animals are fasted 24 hr. before treatment.

Table 1. The Effect of Glucagon on the Metabolic Rate of Rats

No. of rats	Mean body-weight (gm.)	Metabolic rate c.c. O_2 per m.^{2} body surface per min. at N.T.P. (Hr. after injection) 1·0	2·5	4·0	5·5	7·0
		Glucagon				
16	200	205±6*	182±6	165±3	154±4	158±5
		Saline				
16	207	152±5	140±4	135±4	134±3	138±4
		Change (per cent)				
		34·9	30·0	22·2	14·9	14·5
		Fasting + Glucagon				
12	192	133±8	150±5	138±3	138±4	133±4
		Fasting + Saline				
12	190	146±4	125±3	118±2	126±3	125±3
		Change (per cent)				
		25·3	20·0	16·9	9·5	6·4

* Standard error of the mean

A stimulating effect of glucagon on the metabolic rate has not been noted previously. The mechanism(s) involved is (are) not known. It does not appear that hyperglycæmia is a significant contributing factor since in fasting rats glucagon failed to elevate the blood-sugar level but raised the metabolic rate by approximately 25 per cent. Conversely, when hyperglycæmia was induced by administering glucose to intact rats, only a slight increase (4 per cent) in the metabolic rate was observed.

Additional experiments have shown that the calorigenic action of glucagon is greatly reduced by pretreating the animals with dihydroergotamine and is abolished completely by adrenalectomy; thus the possibility that adrenal hormones are involved in this phenomenon merits careful investigation. A more detailed account of these and other experiments will be the subject of another communication.

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Transport of Potassium-42 and Rubidium-86 by Kidney Cortex Slices: the Effect of Varied Concentration Gradients

A comparison of the transport of potassium with that of rubidium has been made in earlier work[1], in which some evidence was obtained that, in contrast to sodium, the transport of both potassium and rubidium across the membrane of renal tubular cells is determined only by electrochemical gradients. A deficiency in this work was that the rubidium content of tissue slices had to be estimated from differences in potassium content as compared with control slices. For this reason, the experiments have been repeated using potassium-42 and rubidium-86, to give a direct estimation, both being present only in the incubating medium (a modified Krebs–Ringer phosphate medium containing the indicated concentrations of potassium and rubidium, with 0·005 *M* alpha-keto glutarate as substrate, at 25° C.). Activity was measured in neutralized nitric acid digests of tissue slice samples, using aluminium dishes, with values corrected for decay, dilution, extracellular space, etc. Since the specific activities of the two isotopes were different by a factor of 4·0, the rubidium

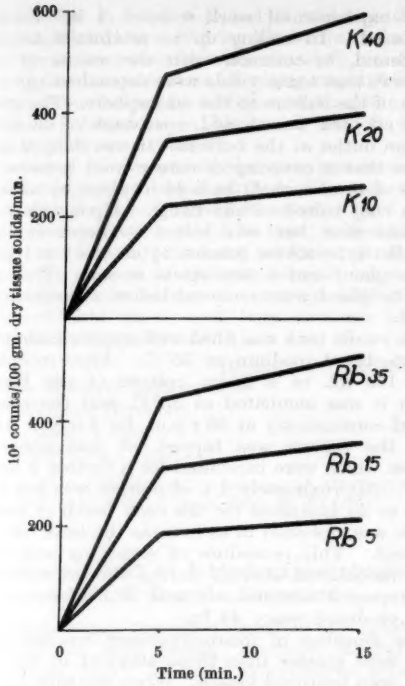

Fig. 1

counts were arbitrarily divided by this factor to give a better comparison of results. Isotope measurements for rubidium-86 in samples containing both potassium-42 and rubidium-86 were carried out five days after the actual experiment, at which time potassium-42 activity was nil. Measurements of potassium-42 activity in tissue samples were not complicated by the presence of rubidium-86. Details of composition of the media are given in ref. 1.

The results are shown in Fig. 1. They extend the previously published evidence that the accumulation of potassium and rubidium after leaching in 0·154 *M* sodium chloride for 2 hr. is exponential in time and linearly related to concentration gradient, and that both cations show the same type of curve.

It appears, then, that under the above conditions, renal tubular cells cannot differentiate between potassium and rubidium. It has been suggested that this is true under physiological conditions[2], and that both cations behave as if passively transported at the cell membrane. This is consistent with the similar particle diameters of the two hydrated cations in aqueous solution (K^+, Rb^+, ~ 3 A.) as opposed to the larger hydrated sodium ion (~ 4·5 A.) which is actively transported by renal tubular cells[3].

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Biosynthesis of γ-Guanidinobutyric Acid from γ-Aminobutyric Acid and Arginine

The recent discovery by Irreverre *et al.*[1,2] of γ-guanidinobutyric acid in mammalian brain and other tissues stimulated research on its biosynthesis and physiological role. Thoai *et al.*[3] have shown that in many invertebrates γ-guanidinobutyric acid is synthesized by the oxidation of arginine through the action of L-amino-acid oxidase. The present communication shows that in mammals it is synthesized by a transamidination reaction[4] involving γ-aminobutyric acid and an amidine donor such as arginine.

Initial experiments showed the activity to be present only in kidney, with rat kidney being more active than that of guinea pig. The localization in kidney, the higher activity in rats than in guinea pigs[4], the requirement for both γ-aminobutyric acid and arginine, the inhibition with parachloromercuribenzoate and the lack of inhibition by cyanide, all suggested a transamidination reaction.

When transamidinase was isolated from pig kidney[5] it was found to catalyse the formation of γ-guanidinobutyric acid from added γ-aminobutyric acid and arginine. Identification of the enzymatically formed γ-guanidinobutyric acid was established using chromatography on paper by comparison with authentic γ-guanidinobutyric acid in two different solvent systems (*tert.*-butanol, formic acid and water, 70 : 15 : 15, and *n*-butanol, pyridine and water, 1 : 1 : 1). Quantitative analysis of the guanidino compound was performed using the Sakaguchi reaction as modified by Van Pilsum *et al.*[6]. Analytical specificity was obtained by the removal of residual arginine by incubation with arginase (Worthington). Arginase was found to have no action on γ-guanidinobutyric acid, β-guanidinopropionic acid and guanidinoacetic acid.

In a typical system containing 1·57 units of enzyme[5], 0·180 μmole of γ-guanidinobutyric acid was formed in 1 hr. β-Alanine was also found to be an amidine acceptor with the formation of 0·068 μmole β-guanidinopropionic acid under the same conditions. With glycine as amidine acceptor, 1·57 μmoles of guanidinoacetic acid were formed in 1 hr. as calculated from a 10-min. incubation when only 0·26 μmole of inhibitory ornithine was formed. Borsook and Dubnoff[4] and Walker[7] were unable to show activity for β-alanine under their experimental conditions. The average relative rates of transamidination for the three acceptors were glycine, 100; γ-aminobutyric, 10; and β-alanine, 3. Incubations were usually performed at 38° C. in tubes containing 20 μmoles arginine, 30 μmoles amidine acceptor, 100 μmoles phosphate buffer *p*H 7·5, in a final volume of 1·5 ml.

In keeping with the general properties of the transamidinase reaction[5,7–9], γ-guanidinobutyric acid was found to be an amidine donor to ornithine or glycine with the formation of arginine or guanidinoacetic acid as revealed by paper chromatography. In other experiments it was found that ornithine was a powerful inhibitor of the arginine-γ-aminobutyric acid transamidination, and that guanidinoacetic acid could be a substitute for arginine as an amidine donor.

Studies on the localization of the enzyme have shown that washed mitochondria have about as much activity as the soluble cellular fraction.

The physiological significance of γ-guanidinobutyric acid is unknown. However, recent reports that

γ-aminobutyric acid may have a role as a neurohumoral agent[10] suggest that γ-guanidinobutyric acid may be similarly involved. Experiments performed by Drs. C. Edwards and S. Kuffler, Johns Hopkins Medical School, Baltimore, have shown that the threshold-level for inhibition of the crayfish stretch receptor is about 7×10^{-4} *M* for γ-guanidinobutyric acid in contrast to 2×10^{-5} *M* for γ-aminobutyric acid. However, no physiological studies have as yet been carried out with mammalian systems.

Full details of the experiments described above will be published elsewhere.

We are indebted to Dr. F. Irreverre for a generous supply of γ-guanidinobutyric acid and for valuable suggestions concerning methodology.

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A Semi-continuous Method for the Large-scale Production of Tetanus Toxin

The production of large quantities of tetanus toxin for human immunization was greatly facilitated by the isolation of the highly toxigenic Harvard strain of *Cl. tetani* by the late Dr. J. H. Mueller and by his success in the provision of a medium suited to this strain. This preliminary report concerns the adaptation of small-scale experimental work to large-scale semi-continuous production, and since it has been possible to reproduce in large vessels the results obtained in 6 in. × 1 in. test-tubes it may be of help to others to describe the lines we have followed and the results that have been obtained.

The Harvard strain of *Cl. tetani* originally isolated by Mueller and Miller[1] was used.

The medium was essentially that of Mueller and Miller[2]. In converting to large-scale work one of the most important factors was found to be the amount of autoclaving to which the medium was subjected, since over-autoclaving may lead to poor toxin titres. When large volumes of 70–150 l. were used the following procedure was adopted. The medium was filled into 15-l. borosilicate bottles, which, after an initial steaming for 90 min., were autoclaved for 15 min. at 117° C. They were then allowed to cool at room temperature and stored in an incubator at 35° C. When required, the medium was siphoned aseptically from these bottles into the growth vessel.

For experimental work 6 in. × 1 in. test-tubes were used. In scaling up to production-levels, it was found, in common with the results of other workers[3], that toxin yields were dependent upon free access of the culture to the atmosphere. The growth vessel adopted was an 80-l. open tank of aluminium with an outlet at the bottom. It was flanged at the top so that a covering of cotton-wool between two layers of muslin could be held in place by an aluminium ring bolted to the flange. Upon this ring a stainless steel bar was bolted to accommodate a propeller-type stirrer (blades $3\frac{1}{2}$ in. × $4\frac{1}{2}$ in.) with a sterile gland and a slow-speed motor. The motor and the gland were removed before autoclaving the vessel.

The sterile tank was filled with approximately 70 l. of autoclaved medium at 35° C. After inoculation with 100 ml. of a 24-hr. culture of the Harvard strain it was incubated at 35° C. and the contents stirred continuously at 60 r.p.m. for 2 days. At this time the culture was tapped off into sterile 10-l. bottles which were incubated for a further 2 days at 35° C. Approximately 1 l. of culture was left in the tank as an inoculum for the next batch of medium which was siphoned in as soon as the tank had been emptied. This procedure of emptying and filling, with mechanical stirring during the growth period was repeated continuously and 70 l. of culture was thus produced every 48 hr.

The densities of micro-organisms reached in the tank were greater than those attained in test-tubes or in open unstirred vessels. When the tank harvests were transferred to 10-l. bottles there was no further increase in density, although, in some cases, gas production continued for several hours. The further incubation served mainly to autolyse the organisms and to release toxin. The toxin values of cultures removed from the tank were initially 0–6 units/ml. and after two days incubation in the bottles reached the maximum values shown in Table 1. In Table 1 the results of three experiments are summarized. In the first, *M* 667, the tank was emptied and replenished every three days; the other two were run on a two-day cycle. The initial low results in the third experiment were due to the use of a poor tryptic digest of casein, which was replaced later by a more satisfactory batch. A feature of the results obtained was the regular fluctuation in the titres of successive harvests. This might be related to the state of the inocula of the batches. In *M* 667, for example, harvests *A* and *C* were partially autolysed and therefore the inocula for *B* and *D* were old and the viable populations present therein were small. It is possible,

Table 1. Semi-continuous Production in Aluminium Tank with Continuous Stirring

	Growth period in tank	Subsequent growth period in bottles	Lf./ml.	L+/ml.	M.L.D./ml.
M 667 *A*	3 days	2 days	30	33	
B			60	70	
C			30		
D			54		
M 689 *A*	2 days	2 days	26		
B			70	72	
M 690 *A*	2 days	2 days	30	33	$1 \cdot 0 \times 10^4$
B			42	45	$1 \cdot 25 \times 10^4$
C			36	36	$0 \cdot 75 \times 10^4$
D			54	57	$1 \cdot 5 \times 10^4$
E			57	57	$1 \cdot 0 \times 10^4$

therefore, that in batches *B* and *D*, which produced the higher toxin titres, the lag phase was relatively long while in the poorer batches *A* and *C*, inoculated with a higher concentration of young organisms, the lag phase was short. In addition to this, the total number of generations in batches *B* and *D* would be higher than in *A* and *C*.

Continuous culture procedures were less successful than the simpler process described above, since the titres obtained did not exceed 40 units/ml. and there was a tendency for the strain to lose toxigenicity.

Since there seems to be some confusion at present as to the units used to evaluate tetanus toxin (due presumably to the change in unit in 1950), it is emphasized that those used here conform to the present international standard.

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Inhibitory Effect of 5-Hydroxytryptophan on Acid Gastric Secretion

WE have recently described the effect of 5-hydroxytryptamine on acid gastric secretion elicited by histamine in dogs[1]. Recent experiments with its precursor 5-hydroxytryptophan have shown that this substance is also capable of inhibiting acid secretion. A technique has been used for recording the secretory-rate from a gastric cannula in anæsthetized dogs, as drops per min. on a kymograph. The acid output is expressed as mille equivalents, and is fairly constant after 1 hr. during histamine administered by continuous infusion (Table 1,*a*).

Infused 5-hydroxytryptamine rapidly lowers the secretory-rate induced by histamine while with 5-hydroxytryptophan there is a latency before secretory and blood-pressure changes. Whereas 5-hydroxytryptamine led to changes in blood pressure and secretion within 2 min. after starting the infusion, there was a delay of 10–15 min. before similar effects were noticed after starting the 5-hydroxytryptophan infusion. Table 1,*b* illustrates the inhibitory effect of varying doses of 5-hydroxytryptophan, and three experiments are recorded which show a marked fall in acid secretory output elicited by histamine, again delayed until the end of the infusion period. Repeated infusions of 5-hydroxytryptophan can be seen to lead to a more prompt inhibition of secretion when given after 2 hr. of histamine stimulation than when given earlier after half an hour of secretion. These effects are very similar to those already found in experiments with 5-hydroxytryptamine.

Dalgliesh and Dutton[2] have recently pointed out that the argentaffin cells of the alimentary tract might be the only source of 5-hydroxytryptophan, the biological precursor of 5-hydroxytrypytamine. The former might be released from this cellular site as a general hormone to be converted locally in various tissue to 5-hydroxytryptamine by specific decarboxylase activity and 5-hydroxytryptophan may thus control the rate of metabolism of 5-hydroxytryptamine. We have inferred by our experiments that 5-hydroxytryptophan leads to an inhibition of gastric secretion due to its conversion to 5-hydroxytryptamine by a mechanism such as this.

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Occurrence of an Amine Oxidase in Horse Serum

MUCH work has been done on the intracellular amine oxidase, a mitochondrial enzyme widely distributed in vertebrate and invertebrate tissues. This enzyme is a catalyst of the biological inactivation of 5-hydroxytryptamine and of the sympathomimetic amines.

In recent years another enzyme has been described in the blood plasma of ruminants which acts mainly on spermine and spermidine, substances which are not oxidized by the intracellular amine oxidase. The spermine oxidase acts slowly also on many amines which are substrates of the intracellular oxidase[1,2].

We have now made observations on a new type of amine oxidase which occurs in horse serum. Horse serum is without significant action upon spermine and spermidine, but we have found that it oxidizes many amines, some rather slowly. These amines include 5-hydroxytryptamine, a number of sympathomimetic amines, cystamine and homocystamine, and some long-chain polymethylene diamines. All

Table 1. (*a*) CONTROL GROUP GIVEN HISTAMINE, TO ELICIT PLATEAU OF SECRETION; (*b*) EXPERIMENTAL GROUP GIVEN HISTAMINE AND 5-HYDROXYTRYPTOPHAN

(Figures are expressed as average acid output in m.eq./15 min. from two 15 min. collections)

	Exp. No.	Dog weight (kgm.)	Dose 5-Htp (μgm./kgm./min.)	Histamine 5 μgm./kgm./min. intravenously, throughout							
				Time in consecutive ½-hr intervals							
				1	2	3	4	5	6	7	8
(*a*) Control group	1	25	—	0·39	2·34	3·03	2·46	2·64	2·75	2·76	2·75
	2	12	—	0·03	1·25	2·41	2·42	2·42	2·45	—	—
	3	15	—	0·13	0·42	0·95	1·11	1·20	1·28	1·16	—
				Infusion 5-Hydroxytryptophan				Infusion 5-Hydroxytryptophan			
(*b*) Experimental group	1	15	5	0·72	1·32	0·65	1·24	0·33	0·24	0·78	—
	2	13	10	1·19	2·10	0·38	0·70	0·37	0·15	0·08	—
	3	18	15	1·29	1·70	0·63	1·82	2·24	0·90	0·20	1·30

these substances are also oxidized by ruminant plasma. Of all the compounds tested so far, benzylamine is the substrate most rapidly oxidized by horse serum. The reaction catalysed is an oxidative deamination, indistinguishable from that catalysed by the intracellular amine oxidase. In its inhibitor specificity the enzyme in horse serum resembles histaminase and the spermine oxidase of ruminant plasma.

In order to distinguish the new enzyme from other amine oxidases, we shall, for the time being, call it benzylamine oxidase. Possibly its main substrate remains to be discovered. However, it is important to remember that, in some mammalian species at least, the blood may take a part in the biological inactivation of amines like 5-hydroxytryptamine or the sympathomimetic amines.

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Choline-Oxidase Activity of Host-Livers of Tumour-bearing Animals

Choline-oxidase converts choline to betaine through an intermediary step of betaine aldehyde formation[1]. Betaine, which is a trimethylglycine, initiates the transfer of methyl groups in stages, with the formation of dimethyl and monomethyl glycine[2]. Since in tumours there is a rapid turnover of nucleic acids[3], it was thought that all the processes, including transmethylation, leading to precursor formation, may also be accelerated. It was thus anticipated that choline-oxidase activity might be higher in the host tissues of tumour-bearing animals. Miller[4] has shown that the overall choline-oxidase activity requires diphosphopyridine nucleotide as an activator, but whether the choline-dehydrogenase or the betaine aldehyde dehydrogenase requires it has not been established[5]. During the course of our studies on tumour–host relationships it was observed that the diphosphopyridine nucleotide-levels in host tissues were considerably diminished[6]. One would anticipate from this a lowering of choline-oxidase activity in host tissues deficient in diphosphopyridine nucleotide. In view of these mutually exclusive and apparently contradictory possibilities it was considered necessary to study the influence of tumour on the levels of choline-oxidase in host tissues.

In the present studies, transplantable Yoshida sarcoma (originally obtained through the courtesy of Prof. H. Druckrey of Freiburg im Breisgau by Dr. A. R. Gopal-Ayengar of this Division), maintained by intraperitoneal transfer of ascites cells in Wistar rats, was used throughout. The tumour grows rapidly and results in the death of the animals in 7–8 days. For the study of choline-oxidase activity, all the animals, controls as well as tumour bearers, were killed by dislocation of the cervical vertebræ on the fourth day after transplantation. Livers were dissected, blotted free of blood, and immediately chilled in ice–salt mixture. The chilled-liver samples were then homogenized in 0·039 *M* phosphate buffer at *p*H 7·4. The final volume was adjusted to contain 1 gm. of liver per 6 ml. of the homogenate. The assay system was essentially the same as used by Williams *et al.*[7]. Endogenous respiration and substrate oxidation were determined by the Warburg technique[8]. To study the effect of diphosphopyridine nucleotide on the choline-oxidase system, 133 μgm. (sigma) were added to each of the Warburg flasks and the rate of oxidation studied for 1 hr. at 37·5° C. The enzyme activity was expressed as μl. of oxygen uptake per hr. per 100 mgm. of dry weight of tissue.

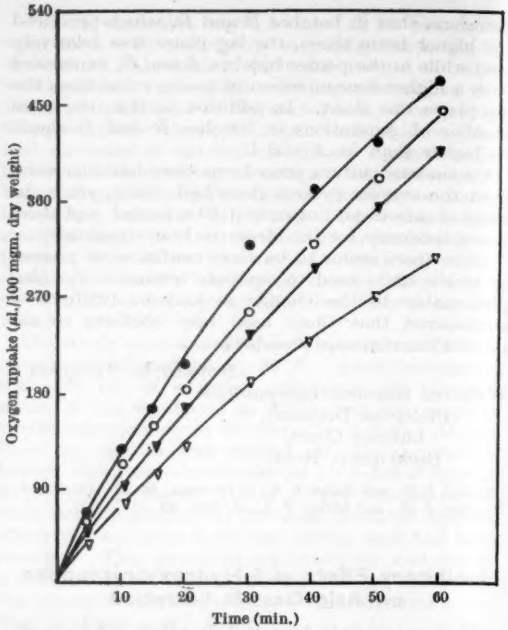

Fig. 1. Substrate oxidation of livers. From normal animals: Control, ○—○; supplemented with 133 μgm. of diphosphopyridine nucleotide, ●—●. From animals bearing Yoshida sarcoma: Control, ▽—▽; supplemented with 133 μgm. of diphosphopyridine nucleotide, ▼—▼

The results of these experiments are given in Fig. 1. It will be seen that the livers of the tumour-bearing animals showed considerably diminished choline-oxidase activity. Endogenous respiration, however, was not appreciably different in the livers from normal and tumour-bearing animals. In substrate oxidation, however, a marked lowering to the extent of 31·2 per cent was seen in the tumour-bearing animals. Thus, while the enzyme activity of the normal livers was 452 μl., the activity of the host livers was only 311 μl. of oxygen per hr. per 100 mgm. of dry weight.

The effect of fortifying the system with diphosphopyridine nucleotide has also been tested. It was found that its addition increased choline-oxidase activity of host liver homogenates by 32·1 per cent while the normal livers showed an increase in activity by 4·0 per cent only. These results suggest that lowering of diphosphopyridine nucleotide-levels may be an important factor in determining the choline-oxidase activities of host livers. In this connexion it is pertinent to point out that adenine is a common precursor of nucleic acids and of pyridine nucleotides. Our previous work has shown that there is a preferential utilization of adenine for nucleic acid synthesis in actively growing tumour tissues, which

probably results in deprivation of host tissues of available adenine for pyridine nucleotide formation[6].

These observations lead us to the conclusion that choline-oxidase activity is not only not increased in host tissues of tumour-bearing animals, but is actually found to be decreased. It appears that the mechanism by which the tumour obtains its increased requirements of precursors for nucleic acid synthesis is not by an acceleration of formation of precursor in host tissues, but by an appropriation of all the available precursors of the body at the cost of depriving the host tissues of some essential metabolites. Neoplasm is unique in this respect, because during its evolution it has acquired the characteristics of maintaining its high rate of growth even in absence of adequate levels of some of the essential co-factors such as pyridine nucleotides, which are so necessary for the economy of normal tissues.

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Natural Occurrence of a New Aldoheptose Sugar

At the present time aldoheptose sugars are known to occur naturally only in bacterial polysaccharides. The first of these 7-carbon sugars was recorded by Jesiatis and Goebel[1] in a *Shigella sonnei* product, and during the past few years it has become increasingly clear that aldose sugars of this series are common constituents of bacterial polysaccharides[2]. Only in three instances have aldoheptoses been isolated and identified; the aldoheptose components of both *Shigella flexneri* and *Escherichia coli* products were shown by Slein and Schnell[3] and Weidel[4] to be L-glycero-D-mannoheptose and in a *Chromobacterium violaceum* (BN) polysaccharide MacLennan and Davies[5] identified D-glycero-D-galactoheptose. In many other polysaccharides the aldoheptose constituent could not be distinguished chromatographically from L-glycero-D-mannoheptose (or its optical enantiomorph D-glycero-L-mannoheptose)[6].

The presence of a 7-carbon sugar in a polysaccharide of *Chr. violaceum* (N.C.T.C.7917) was recorded by Davies[7], but it was not established that it differed from either of the aldoheptoses already isolated. This most unusual polysaccharide contains a sugar of a series not previously known, a 2-amino-6-deoxy sugar[8] recently identified as fucosamine[9]. The aldoheptose constituent has now been found to differ from L-glycero-D-manno- and D-glycero-D-galacto-heptoses (or their optical enantiomorphs).

After treatment of the *Chr. violaceum* (N.C.T.C. 7917) polysaccharide with sulphuric acid–cysteine (Dische test)[10], an absorption peak at 505 mμ was found, which is characteristic of heptose sugars under the conditions used. Examination of acid hydrolysates on paper chromatograms showed the presence of an aldoheptose by the characteristic purple-coloured spot revealed by spraying with anisidine hydrochloride. Using the data on aldoheptose identification already recorded[2] the new sugar could be clearly distinguished from ten of the sixteen D-aldoheptose configurations, these were D-glycero-D-galacto-, D-glycero-L-galacto-, D-glycero-D-gluco, D-glycero-L-gluco, D-glycero-D-allo, D-glycero-D-gulo, D-glycero-D-altro, D-glycero-D-talo-, D-glycero-L-talo- and D-glycero-D-ido-heptoses (or their optical enantiomorphs). Using three different solvent systems (*a*, butanol–pyridine–water, 6 : 4 : 3; *b*, *n*-propanol–benzyl alcohol–formic acid; *c*, 95 per cent (v/v) acetone–water)[2] the new sugar could not be distinguished from D-glycero-D-mannoheptose but the D-glycero-L-manno-configuration could not safely be ruled out. In phenol–ammonia (*d*) the latter travels faster than glucose ($R_{glucose} = 1{\cdot}03$) whereas the former travels more slowly than glucose ($R_{glucose} = 0{\cdot}95$), and using this solvent system it was clear that the new sugar was not D-glycero-L-mannoheptose (or its optical enantiomorph L-glycero-D-manno-heptose, already isolated) but still matched D-glycero-D-mannoheptose (or its optical enantiomorph L-glycero-L-mannoheptose).

Four aldoheptose sugars have not yet been synthesized and are not, therefore, available for direct comparison; these would be the -L-ido, -L-allo, -L-gulo and -L-altro configurations in the D-glycero-series. From data given by Davies[2] the D-glycero-L-ido sugar could be safely excluded, from its expected similarity in behaviour to that of D-glycero-D-ido-heptose in all the solvent systems. By similar reasoning the other three configurations could be regarded as unlikely to match the *Chr. violaceum* (N.C.T.C. 7917) heptose by the expected behaviour of D-glycero-L-alloheptose in solvents *a* and *d*, of D-glycero-L-guloheptose in solvent *d*, and of D-glycero-L-altroheptose in solvents *a* and *c*.

The amount of the aldoheptose sugar present in the polysaccharide cannot be estimated by the Dische method[10] until its identity is firmly established because different aldoheptoses give different amounts of absorption in this test; also D-glycero-D-manno-heptose has not yet been obtained in crystalline form for comparison on a weight basis and is only available in solution. As judged by the appearance of hydrolysates on chromatograms, however, the sugar appeared to be present in an amount of the same order as of the other sugar constituents (glucose, galactose, fucosamine), and estimated as D-glycero-L-mannoheptose gave a figure of about 25 per cent.

The new sugar would thus seem most likely to be D-glycero-D-mannoheptose (or its optical enantiomorph L-glycero-L-mannoheptose from which it would not be distinguishable chromatographically); but it is hoped to establish its true identity by isolation.

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Effect of Prolonged Administration of Reserpine on the Endocrine Glands of the Rat

It has been shown that reserpine influences the anterior[1] and the posterior[2] lobes of the hypophysis, the thyroid gland[3], the adrenal medulla[4] and cortex[5], and the endocrine cells of the gonads[1]. In most of the work on this subject, the short-term effects have been investigated. Therefore, we undertook a study in which the effect of prolonged administration was examined.

Young male rats were injected subcutaneously with 0·04 mgm. of reserpine daily for 2 months. The controls were given the same volume of physiological saline. The animals were killed 9 days after the last injection. Table 1 shows the effect of reserpine on the body-weight and on the size of various organs. Reserpine caused a pronounced retardation of growth, which was statistically highly significant ($P < 0·0001$). The mean kidney-weight of the reserpine rats was significantly lower ($P < 0·02$) than that of the controls. No other significant differences were observed. The lower kidney-weight in the reserpine group is probably essentially due to the retarded growth.

Hypophyses were examined histologically for the cell types in the anterior lobe, using a periodic acid–Schiff trichrome stain, and the posterior lobe for the amount of neurosecretory substance, using Gomori's chrom-hæmatoxylin stain. The thyroids were studied qualitatively for the relative amount of epithelium and colloid, and for the height of the epithelial cells. Distribution of lipids in the adrenal cortex was examined in sudan-stained sections. Adreno-medullary catechol amines were studied with the aid of the chromaffin reaction and formol-induced fluorescence, as well as by quantitative determinations of adrenaline and noradrenaline content. In none of these respects were significant differences found between the reserpine group and the control group.

Table 1

Variable	Reserpine rats (9)		Saline controls (9)	
	Mean	S.D.	Mean	S.D.
Initial body-weight (gm.)	111·1	16·2	95·6	16·7
Final body-weight (gm.)	122·2	24·2	156·1	27·8
Gain in weight (gm.)	11·1	13·6	60·6	15·1
Adrenal weight (mgm.)	12·3	1·0	11·4	1·8
Medullary volume (arbitrary units)	10·1	1·5	9·5	1·4
Thyroid weight (mgm.)	17·6	3·6	16·2	2·2
Testis weight (gm.)	2·19	0·52	2·45	0·16
Kidney weight (gm.)	1·18	0·23	1·45	0·22

Table 2

	Much	Little	Total
Reserpine	0	9	9
Controls	6	3	9
Total	6	12	18

The histological structure of the testis was studied in hæmatoxylin–eosin-stained sections. Normal spermatogenesis was found in all animals, but there seemed to be a tendency towards smaller amounts of interstitial cells in the testis of the reserpine-treated rats. To study this subject more carefully, the testis slides of the control group and those of the reserpine group were mixed. They were then examined in random order for the amount of interstitial cells, using two categories, 'much' or 'little', for the evaluation. The result is illustrated in Table 2, which shows that, even after the precautions taken to avoid subjective bias, all rats of the reserpine group fell into the 'little' group for interstitial cells, whereas six of the nine rats of the controls came into the 'much' group. The probability of such an event occurring by mere chance was calculated using the exact treatment, as described by Fisher[6]. It was thus revealed that the observed difference is statistically significant ($P < 0·005$).

The observations indicate that doses of reserpine sufficient to cause a pronounced arrest of growth have little effect on most endocrine organs 9 days after the discontinued treatment. Failure to confirm earlier reported changes caused by reserpine (see refs. 1–5) is probably explained by the relatively long recovery time, which allowed for the restitution of the normal state. It is the more noteworthy that regressive changes in the interstitial cells of the testis, earlier reported by Tuchmann–Duplessis[1] in reserpine-treated rats, were still persistent.

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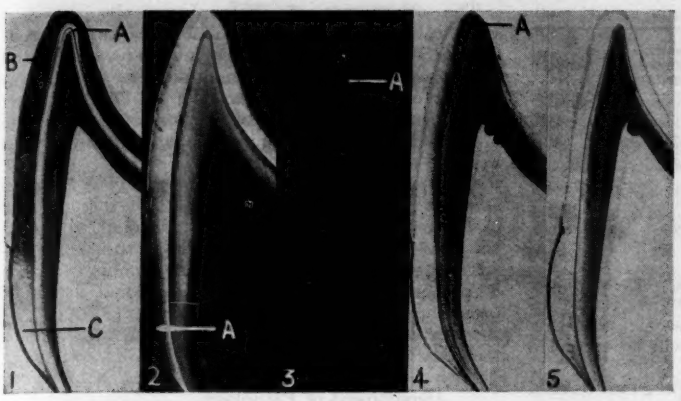
Assessment of Mineral Content in Water-mounted Sections of Dental Enamel

Recently, a new technique for identifying areas of reduced mineral content in ground sections of dental enamel by their light-scattering properties when examined in distilled water, was published[1]. It was shown that when viewed by transmitted



Figs. 1–5. 1, Ground section of a deciduous right maxillary central incisor from two-weeks old infant. Ordinary transmitted light. In distilled water (× 10); *A*, small zone of translucent well-mineralized enamel along the incisal amelo-dentinal junction; *B*, dark opaque zone which has expanded to involve all but the cervical enamel; *C*, cervical zone of poorly mineralized immature enamel which still appears translucent. 2, Microradiograph of same section as Fig. 1. Exposure time 5 min. (× 10); *A*, area of lowest mineral content in the cervical enamel. 3, Microradiograph of same section as Fig. 1. Exposure time 15 min. (× 10); *A*, area of highest mineral content in the incisal amelo-dentinal junction region. 4, Same section as Fig. 1, but partially demineralized. Ordinary transmitted light (× 10); *A*, previously translucent zone along the incisal amelo-dentinal junction now appears opaque. 5, Same section as Fig. 1, but completely demineralized. All parts of the enamel are translucent. Ordinary transmitted light (× 10)

light, areas of reduced mineral content in sections of erupted teeth or teeth in the late stages of development appeared dark and opaque, while normally mineralized mature enamel was transparent or translucent.

During a recent investigation, it was decided to extend the scope of this technique by applying it to ground sections of deciduous teeth in the early stages of development.

100μ-thick longitudinal labio-lingual or bucco-lingual ground sections were prepared from deciduous teeth ranging in age from 26 weeks *in utero* to 18 months postnatal. These sections were placed in distilled water and examined in transmitted ordinary light. Microradiographs of the same sections were then taken and compared with the results obtained in the ordinary light examination. By varying the X-ray exposure time, while keeping all the other factors constant (30 kV., 20 m.amp., copper target, nickel filter), a series of microradiographs was obtained for each section. This procedure made it possible to assess more completely the variations in X-ray absorption within the enamel of any given section as the illustrations show (Figs. 2 and 3). The sections were then demineralized in a routine histological decalcifying fluid composed of formic and citric acid and re-examined in distilled water by transmitted ordinary light.

Using these methods of examination, the following results were obtained. In the early stages of development the undecalcified enamel when examined in water by transmitted light appeared translucent with a faint yellow coloration (Fig. 1,*C*). A dark opaque area then developed in the incisal enamel and with advancing age extended cervically to include all the enamel (Fig. 1,*B*). Finally, a translucent zone appeared in the incisal amelo-dentinal junction area (Fig. 1,*A*) and extended slowly in a peripheral and cervical direction, until the somewhat variable translucent appearance of the mature enamel was attained everywhere.

The microradiographs of the same sections, prior to decalcification, showed that the extent of the zone of high X-ray absorption, and hence the proportion of mineral matter present, steadily increased with age until the mature enamel absorption was reached. This increase in absorption, which was first noted in the incisal amelo-dentinal junction area (Fig. 3,*A*), expanded in a fairly regular peripheral and cervical direction.

During the demineralization of the sections, enamel in the early translucent stage of development remained virtually unaltered. Enamel in the opaque stage of development, however, became translucent and colourless (Fig. 5); and enamel in the later translucent stage of development became opaque (Fig. 4,*A*) and finally translucent and colourless again (Fig. 5).

Correlating these results, it now appears that the relationship between mineral content and the appearance of water-mounted sections of enamel in transmitted light is as follows: (1) areas devoid of mineral matter appear translucent and colourless; (2) areas with a low mineral content appear translucent with a faint yellow coloration; (3) areas with an intermediate mineral content appear dark and opaque; (4) areas with a high mineral content, but not necessarily fully mineralized mature enamel, appear translucent and colourless.

Translucency in water is therefore not a reliable indication of high mineral content when ground sections of enamel in the early stages of development or advanced stages of demineralization are being examined.

A full account of this investigation will be published later.

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Incidence of Abnormal Hæmoglobins in Jamaica

Widespread studies have been carried out in Africa concerning the incidence of the abnormal hæmoglobins *S* and *C*, showing a very different geographical distribution for these two[1].

From the sixteenth until the early nineteenth century the slave trade brought large numbers of Africans to the North American continent and to the Caribbean territories, where these Africans are still found in a relatively pure state. In the United States there have been several reports on the incidence of hæmoglobins *S* and *C*[2]; in the Caribbean only one

Table 1

	No.	*S* gene	*C* gene	Average hæmoglobin (gm. per cent)	Range
Genotype *AA*	878	0	0	11·2	6·6–15·0
Genotype *AS*	106	106	0	11·2	7·8–13·2
Genotype *AC*	30	0	30	11·3	8·6–14·7
Genotype *SC*	2	2	2	11·6 10·3	
Genotype *SS*	1	2	0	8·0	
Genotype *S*-Thal.	1	1	0	12·5	
Total *S* genes		111 (10·9 per cent)			
Total *C* genes		32 (3·1 per cent)			

report on the incidence of sickling has appeared hitherto[3]. Further studies in this region were considered to be important. This is the second report on work done in Jamaica. This work will be extended to other islands in the Caribbean.

The people investigated were 1,018 pregnant women who attended the ante-natal clinic of the University College Hospital. This group was selected because blood samples were taken routinely and it represented a random sample of the population around Kingston, comprising about one-fifth of the total Jamaican population. All the blood samples were subjected to paper electrophoresis of hæmoglobin[4]. A sickling test was done on all specimens which gave an *AS* pattern. This sickling test was positive in all cases, thereby excluding hæmoglobin *D* in our group.

The results are given in Table 1. A possible fallacy arising out of studies on the distribution of genetic factors should be stressed. When the incidence of a given gene is low, for example, the *C* gene in my series, then quite erroneous results can be obtained when only small numbers are studied. For example, in the first 400 women investigated, I found 19 with a *C* gene (4·7 per cent); in the last 400 I found only 7 (1·7 per cent).

A correct evaluation of racial mixtures occurring in the group was impossible; but it seems likely that it consists of about 90 per cent pure Negro and 10 per cent Negro mixed with White, Chinese and Indian. These percentages are based on the 1946 census figures in Jamaica. The gene frequencies given in Table 1 would therefore have been slightly higher had it been possible to select Negroes only.

Accepting that the gene frequencies in Table 1 are correct for the population as a whole, then one would expect that, of every 1,000 children born, 3 would have true sickle-cell anæmia (genotype *SS*) and 1·6 would have sickle-cell hæmoglobin *C* disease (genotype *SC*). The incidence as it was found for the genotype *SC*(2) fits very well with the expected figure.

This suggests that the mortality in this genotype is not materially different from the mortality in the population as a whole.

From our knowledge of the survival-rate in true sickle-cell anæmia[5] it is clear that one would expect to find in adults a much lower incidence than the calculated one in this condition. In addition, it is probable that if a woman with sickle-cell anæmia reaches the age of reproduction she will be less fertile or that very early abortion will occur. The one case of true sickle-cell anæmia found in my series is remarkable in that she has had three healthy children in four pregnancies and is pregnant again. We could prove beyond any doubt that she has the genotype *SS* from studies on her three children, seven siblings and both parents[6].

The other case of electrophoretically apparent sickle-cell anæmia was found in fact to be heterozygous for the *S* gene (from the father) and to have inherited from the mother a thalassæmia-like gene which gave rise to fœtal hæmoglobin-levels of 24, 26 and 16 per cent respectively in her mother, her brother and one of her children[7]. The only other hæmoglobin present in these three was hæmoglobin *A*.

Another fact emerging from this study is that the average hæmoglobin-levels for the first three groups in Table 1 are identical. This is additional proof that the possession of the *S* trait or the *C* trait is no disadvantage to a person so far as hæmoglobin synthesis is concerned, even under the additional stress of pregnancy.

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Specific DDT-Resistance in Houseflies

Two strains of houseflies (*Musca domestica* L.) have been derived by selection for a number of generations from a DDT-susceptible colony which originated from wild flies collected in 1939. The colony had been mass-reared in the laboratory for fourteen years without exposure to insecticides. Selection was by two different methods. One strain (*D*) was derived by incorporating DDT wettable powder in the larval medium at 80 p.p.m. DDT for the first three generations, 160 p.p.m. for generations 4–9, and 320 p.p.m. for all subsequent generations. The other strain (*L*) was started ten generations later than *D*; it was selected on the basis of slow pre-adult development, that is, by breeding only from flies emerging from the cultures towards the end of the emergence period, and its breeding stock was not exposed to insecticides. Pimentel *et al.*[1] had found that late-emerging flies were more tolerant of DDT than early emerging ones, and that, in four DDT-resistant strains, resistance was associated with prolonged larval period.

As selection proceeded, the susceptibility of the strains to DDT was determined periodically by dosage-mortality tests in which batches of 40 flies of each sex, 5–6 days old, were dosed with six DDT-kerosene solutions applied by microburette[2] to their mesonota. 'Dioxan' was used as auxiliary solvent when necessary. The volumes applied were of the order of 0·08 and 0·13 µl. for males and females respectively, with slight variations to compensate for differences in batch weights. Treated flies were supplied with 10 per cent sucrose solution and held at 25° C. for mortality counts at 24 hr. after treatment. For comparison the unselected parent strain (*U*) was similarly tested.

Both selected strains developed significant resistance to DDT. After an initial rapid rise during the first four generations, resistance showed no further change of a major nature for thirty subsequent

Table 1

	Strain *U* Male	Strain *U* Female	Strain *D* Male	Strain *D* Female	Strain *L* Male	Strain *L* Female
*LD*50* DDT	5	7	70†	110†	42	65
*LD*50 DDT + DMC (1 : 1)				27†	6·5	12·9
*LD*50 *gamma*-BHC	0·6	0·8	0·6†		0·4	0·6
*LD*50 allethrin	7·6	12·9			7·6	13·0
*LD*50 diazinon	0·4	0·6			0·6	0·7
*LC*50‡ sodium arsenite	0·07	0·07	0·05†	0·05†	0·07	0·06
DDT recovered (μgm.)	364	382	298	313	308	327
DDT dehydrochlorinated (μgm.)	0	6	67	51	82	64
Total recovery (per cent of initial DDT)	91	97	91	91	98	98
*LD*50 DDT	4·9	6·6	41	85	46	86
*LD*50 DDT			77†	155†		

* All *LD*50's as μgm./gm. of flies.
† Test flies reared in medium containing DDT.
‡ Per cent w/v causing 50 per cent mortality in 17 hr.

generations, during which it fluctuated within the ranges $R_D = (15 \pm 5)R_U$ and $R_L = (11 \pm 3)R_U$, where R_U, R_D and R_L are the *LD*50's for the respective strains.

In thirty successive generations, strains *D* and *U* were compared with respect to the time from oviposition to maximum daily emergence of adults. No significant difference between the strains was found. A similar comparison of strains *L* and *U*, over sixteen generations, indicated that a selection had retarded pre-adult development by a significant mean amount of 1·6 days.

Resistance in strain *D* was expected to be specific for the DDT type of insecticide, since DDT had been the sole selective agent. No evidence of increased tolerance to the BHC group of chlorinated hydrocarbons[3] was found in tests with γ-BHC applied by the same topical dosing method, or to sodium arsenite fed in sucrose solution. Strain *L*, which had not been selected with DDT, was tested more extensively, and was found to be non-resistant to γ-BHC, allethrin, diazinon and sodium arsenite. (McKenzie and Hoskins[4] have also found a similar specific DDT-resistance in their substrains selected for late pupation.) The toxicity of DDT to the resistant strains was increased considerably by the synergistic action of DMC, this compound being much less toxic than DDT when applied alone[5]. The results (first part of Table 1) indicated that a similar type of specific DDT-resistance had developed in both selected strains.

Since DMC had been shown to inhibit the dehydrochlorination of DDT by resistant flies[6], the three strains were examined for the presence of DDT-dehydrochlorinase[7]. Acetone–ether powders were made from 10-gm. samples of 5–6 day old flies of each sex. The test flies of strain *L* were taken from the eighteenth generation, those of strain *D* from a special twenty-eighth generation culture containing no DDT. Samples of buffered aqueous extracts of the powders, each equivalent to 40 flies, were incubated under nitrogen with 400 μgm. of DDT (deposited on glass chips) in the presence of glutathione for 6 hr. at 37° C. Cyclohexane extractions were then carried out and the amounts of unchanged and dehydrochlorinated DDT determined spectrophotometrically. Concurrently, the susceptibility of each strain to DDT was determined. In strain *D*, flies grown in medium with and without DDT were both tested. The *LD*50's thus obtained are grouped with the enzyme test results in Table 1 (second part).

In strain *D* the test flies reared in DDT-medium showed normal resistance for this strain, but exclusion of DDT from the rearing medium resulted in a fall in resistance to the same level as that of strain *L*. Extracts of flies of both resistant strains showed significant enzyme activities of a similar order. Comparing the sexes, in both strains males were less resistant, but showed higher enzyme activities than females—a non-conformity which remains unexplained. As expected, enzyme activity in the DDT-susceptible strain *U* was insignificant. Since the selected strains developed similar enzyme activity and DDT-resistance, although selected by different methods, it seems likely that enzymatic dehydrochlorination of DDT was the major factor in resistance.

The occurrence of DDT-dehydrochlorinase and specific resistance to DDT in strain *L* has some interesting implications. It establishes that production of the enzyme is not necessarily dependent on a stimulus from DDT in the environment, and it precludes any possibility that this type of resistance is due to a mutagenic action of DDT. The function of the enzyme in flies of strain *L* which had never been exposed to DDT is not known.

Concerning the origin of resistance in the two strains, the fact that on two occasions, ten generations apart, resistance began to develop immediately selection was started suggests that the parent colony contained a self-propagating small proportion of abnormally DDT-resistant individuals already possessing the enzyme, and that this proportion was increased by selection, either with DDT or for slow pre-adult development, until it constituted a majority in the resistant strains. If a functional relationship exists between DDT-resistance, due to the possession of the enzyme, and rate of pre-adult development, it is at present obscure, since the flies of one resistant strain (*D*) showed no sign of retarded development, while those of the other (*L*) were significantly slower in development.

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Infectivity of Influenza Virus Filaments

Although the presence of filamentary forms in preparations of influenza virus was first noted in 1946 [1], the finding remained one of academic interest until the demonstration by Chu, Dawson and Elford in 1949 [2] that recently isolated influenza *A* strains contain a high proportion of filaments. These forms have since been shown to possess many of the biological characteristics of spherical influenza virus particles[3,4]; but the question of the number of filaments needed to induce infection was not considered until recently. The main contribution in this direction has been the pioneer work of Donald and Isaacs[5], who used quantitative counting techniques. They, however, did not claim any differences in the relative infectivity of virus filaments and spheres. Valentine and Isaacs[6] have since suggested that, owing to the tendency of filaments to break up during adsorption on red cells, the actual counts of Donald and Isaacs[5] are over-estimates of the number of filaments initially present, and hence there is an increased probability that filaments are infectious. In connexion with nucleic acid studies on filaments, we have used a strain of filamentary virus (Ryan) that has a mean ratio of 50 per cent egg infectivity dose/agglutinating dose of the same order as that given by strains which exist almost exclusively as spheres. Using the counts of Donald and Isaacs[5] together with our 50 per cent egg infectivity dose/agglutinating dose value, it can be calculated that, for this strain of virus, fewer filaments than spheres are necessary to induce infection in the embryonated egg.

The *A* strain Ryan was isolated from the 1954 influenza epidemic in Melbourne. It has been passaged sixteen times at limit dilution in eggs. Following inoculation of 0·05 ml. at a 10^{-3} dilution into 10-day embryonated eggs, the allantoic fluid was harvested after 72 hr. incubation at 35° C.; the classical *A* strain *PR*8 was grown and all hæmagglutinin and infectivity determinations carried out as described previously[7]. These techniques are similar to those used by Donald and Isaacs[5]. In nineteen experiments, the mean ratio ($\log_{10}$) 50 per cent egg infectivity dose/agglutinating dose value for Ryan was $6{\cdot}0 \pm 0{\cdot}5$; in twelve experiments, for *PR*8, $6{\cdot}0 \pm 0{\cdot}3$. The average proportion of filaments in Ryan allantoic fluid is 30 per cent; their morphology is similar to that of filaments in *A*/Persian Gulf/2/52 [5] and upon fragmentation there is an increase in hæmagglutinin. Donald and Isaacs[5] have shown that the ratio ($\log_{10}$) of particles to agglutinating dose for non-filamentary strains is $7{\cdot}2 \pm 0{\cdot}13$ (that is, 16×10^6 particles = 1 agglutinating dose) while for a strain in which the proportion of spheres to filaments is approximately 50 : 50, the ratio ($\log_{10}$) is $6{\cdot}6 \pm 0{\cdot}08$ (that is, 4×10^6 particles = 1 agglutinating dose). In the latter case, the contribution due to the spheres is 2×10^6 particles, which is $\frac{1}{2}$ of the agglutinating dose given above for *PR*8. Hence that due to the 2×10^6 filaments is $\frac{1}{2}$ agglutinating dose. Thus in a preparation containing filaments only, $2{\cdot}3 \times 10^6$ units = 1 agglutinating dose. From this, it can be calculated that in a preparation containing 30 per cent filaments, $6{\cdot}1 \times 10^6$ particles = 1 agglutinating dose, that is, $10^{6{\cdot}78}$.

The ratio ($\log_{10}$) particles/agglutinating dose for *PR*8 = 7·2; for Ryan = 6·78. The ratio ($\log_{10}$) 50 per cent egg infectivity dose/agglutinating dose for *PR*8 = 6·0; for Ryan = 6·0 Therefore, the ratio ($\log_{10}$) particles/50 per cent egg infectivity dose for *PR*8 = 1·2; for Ryan = 0·78. The number of particles/50 per cent egg infectivity dose for *PR*8 = 16; for Ryan = 6·1.

Of this figure 6·1 for Ryan, 70 per cent or approximately four particles are spheres and contribute a quarter of the 50 per cent egg infectivity dose. Therefore, two or three filaments are equivalent to one 50 per cent infectivity dose. In view of the finding[3,4,6] that filaments break down during manipulation, it appears possible that one filamentary particle as present in unharvested allantoic fluid may induce infection.

This calculation assumes that the spheres present in Ryan preparations have the same relative infectivity as *PR*8 spheres. Two observations support this. (1) The value of the ratio 50 per cent egg infectivity dose/agglutinating dose for spheres isolated by filtration from *A*/Persian Gulf/2/52 was not appreciably different from that of the allantoic fluid preparation[5]. (2) In three preparations the value of the ratio ($\log_{10}$) 50 per cent egg infectivity dose/agglutinating dose of a strain of Ryan, derived from the parent strain by passage at low dilution and containing very few filaments[4], ranged from 6·2 to 5·9.

The finding that considerably fewer filaments than spheres are needed to induce infection has a number of important implications. These will be discussed in conjunction with the results of the nucleic acid studies in a paper to be published elsewhere.

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Structure of Molluscan Tropomyosin

Certain molluscan smooth muscles contain protein filaments with a regular and characteristic fine structure[1–3] to which the name paramyosin has been given[4]. Neither the chemical nature nor the function of these filaments is understood, and attention is once more drawn to these problems by the recent discovery in the same muscles of an asymmetric globulin[5,6] precipitating in the form of needle-shaped 'crystals'. This was found[6–8] to have the amino-acid pattern of a tropomyosin, and the large amounts present in slow lamellibranch adductor muscles suggested that it might be responsible for the paramyosin structure, an inference supported by some preliminary studies of the X-ray diffraction pattern[5,7]. These 'crystals' have now been studied by electron microscopy.

The protein was usually made from the white part of the adductor muscle of the oyster (*Gryphaea angulata*), but similar results were obtained with the equivalent muscle of *Pinna nobilis*. Fresh muscles were homogenized in 0·04 *M* potassium chloride buffered at

*p*H 7·0 with 0·0067 *M* Sörensen phosphate buffer. Microscopic examination showed that the muscle fibres had been broken up and many paramyosin filaments released; these are visible in a phase-contrast microscope with an objective of *N.A.* 1·3. The homogenate was washed twice in a large volume of the same weak potassium chloride solution to remove water-soluble proteins; centrifugation at about 2,000*g* brought down all the filaments. The washed homogenate was then suspended in 1·0 *M* potassium chloride buffered at *p*H 7·0 with 0·0067 *M* phosphate buffer, and again centrifuged at 2,000*g*. The supernatant protein solution, which contained no visible filaments, was dialysed[4] against a series of potassium chloride solutions (0·75, 0·5, 0·3 and 0·15 *M*), all of them buffered at *p*H 7·0 with 0·0067 *M* phosphate buffer. The small amorphous precipitate which formed at 0·3μ was removed. Needle-shaped 'crystals' were precipitated at 0·15μ and were placed on grids bearing carbon films. They were fixed and stained for two minutes with an unbuffered 0·1 per cent aqueous solution of phosphotungstic acid and then washed with water. The preparations were studied in a Siemens 'Elmiskop I'.

The long needles are transversely striped and several different band patterns are found. The simplest pattern (Fig. 1) repeats every 145 A. and the bands are demarcated by fine dense lines. All the other patterns repeat every 725 A., and are elaborations of the simple pattern in which certain bands or pairs of bands are denser than the others; in each of these modified bands the dense material lies mainly next to the two lines that demarcate it (Fig. 1).

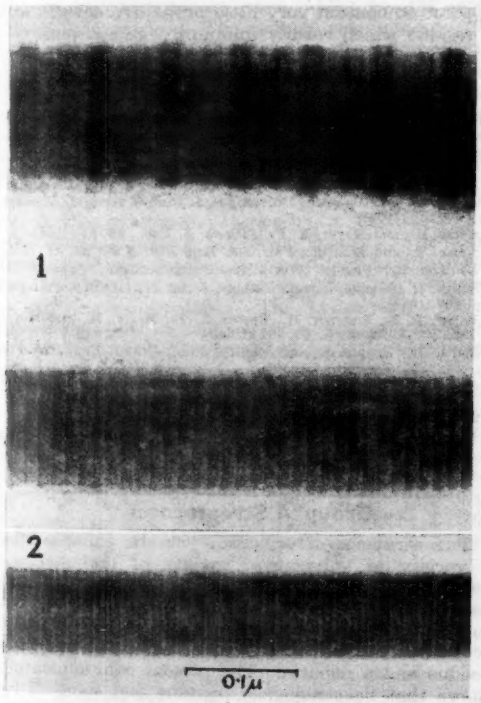

Fig. 1. Two 'crystals' (lying side by side) of water-insoluble tropomyosin from the white adductor muscle of the oyster

Fig. 2. A paramyosin filament isolated from the white adductor of the oyster

Tropomyosin needles with the simple pattern show a banding which very closely resembles that of paramyosin filaments isolated from the same muscles and fixed and stained in the same way (Fig. 2). We find that the pattern of dots described in the original account[2] of paramyosin structure appears only when the filaments are beginning to dissolve.

The tropomyosin needles with the 725 A. period somewhat resemble 'paramyosin-long-spacing', the name given by Hodge[9] to 'crystals' precipitated from solutions of structural proteins extracted from the adductor muscles of *Venus mercenaria*. However, Hodge used a different method to extract the protein and to precipitate it.

At the molecular level, the tropomyosin of *Pinna nobilis* has been studied by light-scattering, sedimentation, diffusion and viscosity methods. Theoretical considerations have led one of us (C. M. K.)[10] to propose that the protein is rod-like, of length 1400 A. and only 19 A. in width. The length is thus twice that of the paramyosin period and equal to that of the 1400 A. band structure of Hodge's[9] acid-reconstituted 'paramyosin-long-spacing' fibrils. For a molecular weight of 134,000, the protein is one of the most asymmetrical yet discovered, and probably exists for the greater part of its length in the α-helical configuration of Pauling and Corey.

The simplest hypothesis to account for all the present findings is that paramyosin and water-insoluble tropomyosin are identical. The fact that the band patterns of the re-precipitated material are variable is not inconsistent with this suggestion. A similar phenomenon is well known in the case of collagen where, according to Schmitt[11], it is due to different modes of aggregation of the same macromolecules.

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Lethality for Guinea Pigs of Ultrasonic Extracts of *Pasteurella pestis*: its Relationship to Death of Guinea Pigs from Plague

A puzzling feature of studies on the basis of pathogenicity of *Pasteurella pestis* is the relationship of the behaviour of the so-called toxin[1-4] in guinea pigs to infection in the same host. This toxin is lethal for mice but not for guinea pigs[4,5], although the two hosts are equally susceptible to plague[1,6]. This anomaly led us to consider whether, in plague, guinea pigs are killed by a toxin different from that killing mice, or whether the 'toxin' as previously isolated is a degraded form of a native toxin that kills both species. The results described below support the latter view and give a reasonable explanation for the death of guinea pigs from plague.

Our work had two main innovations: (1) *P. pestis* and its extracellular products were obtained from infected guinea pigs and examined for any lethal component possibly absent from artificial cultures as was the anthrax toxin[7]. (2) The extraction of the organisms was milder and more complete than the saline extraction of acetone-dried organisms[3,8] or the autolysis of cells by prolonged incubation[1,2,4,5] hitherto employed.

Organisms were separated from the body fluids of guinea pigs which died from infection with *P. pestis* (strain *L*.37) by the methods described[9] for the collection of *Bacillus anthracis* grown *in vivo*.

The sterile filtered plasma from dying guinea pigs which originally contained $1–3 \times 10^9$ organisms per ml. had a small but variable toxicity for mice (*LD*50 > 1 ml.; 0·1 ml. given intravenously) and no detectable toxicity for guinea pigs (10 ml. given intravenously). For the following reasons, it was concluded that no purely extracellular toxin was produced *in vivo* by *P. pestis*, and that the slight toxicity of the plasma resulted from the liberation of intracellular material. First, the toxicity was absent or minimal if the plasma collected from a dying animal was rapidly cooled and filtered. Secondly, there was an increase in toxicity if the unfiltered plasma was stored at 0°.

Attention was turned to the organism as a source of toxin. Treatment with ultra-sonic waves proved the most satisfactory method of breakdown. Organisms grown *in vivo* were suspended in water (10^{10} per ml.) and subjected to ultra-sonic waves (Mullard Ultrasonic Generator, 2 megacycles per sec., 500 watts) at + 3° for 1 hr.; the organisms were mainly disintegrated and after centrifugation the extract was filtered through 'Millipore'.

Several batches of the filtrate (1 ml. = 1×10^{10} organisms) had a mouse (20 gm.) *LD*50 of 1/800 ml. (given intravenously) and when 2,000, 4,000 and 8,000 mouse *LD*50 were injected intravenously into guinea pigs (250 gm.) death-rates of 3/11, 8/10 and 5/5 respectively were obtained. Hence, the *LD*50 for a guinea pig is about 3,000 times larger than that for the mouse. On a body-weight basis, the resistance of a guinea pig to this toxic extract is about 250 times that of a mouse. This ratio is far smaller than the 5,000 indicated from the figures quoted by Schar and Meyer[4] for their plague 'toxin' and that indicated by the statement of Schar and Thal[5] that even in amounts of 300,000 mouse *LD*50 the plague 'toxin' never exerts a lethal effect on guinea pigs.

It seems, therefore, that the same toxin can be responsible for the death of guinea pigs and mice. The species difference in susceptibility of 250-fold is of the same order as that obtained with some other toxins[10]. In both mice and guinea pigs the toxin acted quickly; deaths occurred mainly within 12 hr. with clinical signs of shock and the presence of exudate in the body cavities. Furthermore, the *LD*50 of our toxic extract for guinea pigs was obtained from approximately 4×10^{10} organisms, which number is less than the total *P. pestis* organisms (at least $5–16 \times 10^{10}$) present in a guinea pig (250 gm.) killed by plague.

The properties of the toxic extract described above raise doubts as to whether the toxin as previously isolated is the true toxin of *P. pestis*. This is underlined by the finding that similar extracts have now been obtained from organisms grown *in vitro*. Thus, ultra-sonic extracts of organisms obtained from shaken cultures (28°) of *P. pestis* (strain *L*.37) in a medium similar to that of Higuchi and Carlin[11] (30 hr.), and another medium used by Davies[12] (40 hr.) killed, respectively, 2/4, 3/3, 1/1 and 2/8, 3/12, 7/8 guinea pigs (250 gm.) when 2,000, 4,000 and 8,000 mouse *LD*50 were injected intravenously. It appears, therefore, that *P. pestis* contains a toxic complex which hitherto has only been isolated in part due to deficiencies in previous methods of extraction.

The continued use of ultrasonic waves to form more complete extracts of *P. pestis* than hitherto examined may well shed light on other chemical aspects of the pathogenicity and immunity to plague. Already the technique has been the means of separating *P. pestis* grown *in vivo* into two constituents, namely, the highly toxic soluble material which appears to contain very little protective antigen and a residue which readily immunizes guinea pigs.

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Enhancement of Mouse-virulence of Group A Streptococci

The virulence of organisms can be enhanced by a variety of substances, mainly of carbohydrate nature (see review by Olitzki[1]). Current interest centres on mucin, which was found by Smith and his co-workers[2-4] to owe its activity to the synergic action of three factors—viscosity, a particulate residue and a heparin. The present communication shows that bacteriological peptone and some of its hydrolysis products also have considerable virulence-enhancing activity.

It was first observed that the minimal lethal dose (*LD*100) of group *A* streptococci injected intra-

peritoneally into mice was considerably reduced when organisms were suspended in broth instead of saline: the reduction was of the order of a thousand times. The effect was observed only when organisms and broth were both injected intraperitoneally.

All experiments were carried out on *W*-Swiss mice weighing 25–35 gm. 18-hr. old broth cultures of mouse-pathogenic group *A* streptococci were used; all injections were made intraperitoneally and the volume kept constant at 0·5 ml. The *LD*100 of the cultures in saline was 0·5 ml. of a 10^{-2} suspension, the *LD*50, 0·5 ml. of a 10^{-3} suspension; 0·5 ml. of a 10^{-5} suspension was invariably non-lethal. Animals died within four days and group *A* streptococci were recovered from the heart blood. In control mice broth and peptone caused shock; neither they nor any of the subsequent virulence-enhancing preparations by themselves killed mice.

Viable counts[5] of broth and saline suspensions yielded the same number of colonies suggesting that the reduction of the minimal lethal dose was not due to the streptococci dying in saline. Evidence that a true virulence-enhancing mechanism was involved was given by the fact that broth, injected intraperitoneally as much as 1 hr. after a non-lethal saline suspension of organisms (0·5 ml. of a 10^{-5} suspension), converted the non-lethal dose into an *LD*100.

The constituents of the medium were next examined. The medium consists of 2 per cent 'Oxoid' peptone, 0·8 per cent 'Oxoid Lab. Lemco' broth powder, 0·2 per cent glucose, and 0·2 per cent sodium bicarbonate in distilled water; the glucose and bicarbonate were added to the autoclaved basal medium. The peptone was found active, 0·25 mgm. giving the virulence-enhancing effect; other peptones—B.D.H., 'Difco Bacto' and 'Difco Proteose'—were equally active. 'Lab. Lemco' broth powder was also active, the activity corresponding roughly to the peptone content of the preparation as indicated by the makers. Glucose and sodium bicarbonate were inactive.

Peptone, as the most active constituent of broth, was further examined. It was hydrolysed for 24 hr. with constant-boiling hydrochloric acid. The total hydrolysate, after removal of acid and readjustment of *p*H to 7·4, was as effective in enhancing virulence as the original peptone. The hydrolysate, which contains an acid-insoluble fraction generally referred to as humus, was then centrifuged. The supernatant showed only slight activity. Of 22 individual amino-acids examined only 4 were active, L- and DL-aspartic acid at 0·5 mgm. per mouse, L-lysine, DL-threonine and L-tryptophan at 5 mgm. On the other hand, the sediment, when washed with saline and extracted into sodium bicarbonate, proved most active: weight for weight it was a hundred times more active than peptone. As little as 2·5 μgm. reduced the *LD*100 from 0·5 ml. of a 10^{-2} dilution to 0·5 ml. of a 10^{-5} dilution.

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Duration of Spermatogenesis in the Mouse

A RISE in frequency of dominant lethals in matings at successive intervals during the first few weeks after irradiation of male mice has been observed by Brenneke[1] and Hertwig[2] for X-rays, and by Russell *et al.*[3] for neutrons. Thus Bateman's[4] results with exposure to 200 r. of X-rays confirm the earlier observations. Bateman's[4] interpretation of his data and the subsequent discussions by Auerbach[5] and Sirlin and Edwards[6] concern the determination of the stage in which gametes available at successive weeks were irradiated. As emphasized by Auerbach[5], and now accepted by Bateman[7], Bateman's results[4] do not contradict the essentially parallel response of mice and *Drosophila* that had been partially demonstrated in the earlier work. However, in spite of the attention this subject now has received, several points need clarification, especially in relation to the description and timing of normal spermatogenesis in mice.

First, a point that is mentioned frequently is the possibility of a bias in estimates of the duration of spermatogenesis obtained from irradiated material. A discussion of this point is presented in my paper on the duration of spermatogenesis[8], but does not appear in the advance abstract from which Sirlin and Edwards[6] obtained my estimate of 34·5 days for the duration of spermatogenesis. Sirlin and Edwards[6] state that it is possible that this figure is "increased by delay due to irradiation". Auerbach[5] also states that in Bateman's experiment with 200 r. ". . . spermatocytes are probably not killed—although their development may be somewhat delayed. . . ". Experiments both by other investigators and by us indicate that doses as high as 1,000 r. have no retarding effect on meiosis, or on spermiogenesis of cells irradiated as spermatids. Maturation of spermatids arising from cells irradiated as spermatocytes probably is retarded at high doses, but not by 100 r. Furthermore, we have found the timing, based on irradiations with 100 r., to be completely reliable in experiments where doses as low as 5 r. of gamma-rays from cobalt-60 have been used. We have concluded, therefore, that our estimate of 34·5 days for the duration of spermatogenesis is not seriously biased.

Most of the confusion in description of normal spermatogenesis and in interpretation of irradiation effects results from misclassification of preleptotene spermatocytes. On the basis of their morphology, these cells have been mistaken by various authors for type *B* spermatogonia and for type *A* spermatogonia. Yet in terms of both developmental potentiality and radiation response[9], they are clearly primary spermatocytes. A further confusion, arising from terminology, can be avoided if one retains the definition of primary spermatocytes long accepted by cytologists, and recently emphasized by Hoffman[10] and by Tobias[11] as ". . . those cells which arise after the last mitotic division of spermatogonia and become transformed after the first meiotic division into secondary spermatocytes". This restricts the term 'spermatogonia' to cells capable of mitosis.

It at first appears as if the estimate of the duration of spermatogenesis obtained[12] by labelling adenine with carbon-14 does not agree with our results based on irradiation with 100 r. The results are in agreement, however, if the proper correction is made for

identification of cell stages initially labelled. Ortavant[13] concluded that the uptake of phosphate (labelled with phosphorus-32) occurs primarily in preleptotene spermatocytes, and that estimates of the duration of spermatogenesis obtained by this method must be corrected to include the time required for spermatogonial divisions. The photomicrographs (Fig. 4) of Pelc and Howard[12] strongly suggest that they have misclassified primary spermatocytes as "resting spermatogonia". In addition, cells identified by Sirlin and Edwards[6] simply as "early meiotic prophase", "early spermatids" and "free sperm in the tubules", are not adequately defined, for in the mouse meiotic prophase requires 12½ days, spermatid stages 9½ days, and the last four stages of spermiogenesis (easily confused with mature sperm in routine staining) require 5½ days for completion. Exact definition of cell stages, most easily obtained by use of periodic acid–Schiff staining, must be used in the interpretation of autoradiographs before accurate estimates of the duration of spermatogenesis can be obtained by tracer techniques. Confusion over identification of cell stages labelled by adenine containing carbon-14, and inadequate definition of reference points selected in stages of several days duration, easily account for the fact that the second column in the table of Sirlin and Edwards[6] does not agree with our results. It is apparent that correct interpretation of the tracer technique would give better agreement.

The first column of the table presented by Sirlin and Edwards[6], which is based on an advance abstract of my results, also needs revision, because the relative frequency of tubule stages in the rat[14] cannot be applied to the mouse. Sirlin and Edwards incorrectly state that Roosen-Runge and Giesel[15] and Leblond and Clermont[14] " . . . determined the relative durations of the spermatogenic stages in the normal rat and mouse. . . ". The quantitative results given by these authors are based exclusively on the rat. The only published results available on relative frequency of stages in the cycle of the seminiferous epithelium of the mouse are given in my recent paper[8]. The fact that the relative frequency of tubule stages in the rat cannot be applied directly to the mouse should have been apparent from an earlier publication[16], where it was shown that only twelve stages can be identified in the mouse instead of fourteen as described for the rat.

In order to clear up the confusion over estimation of duration of stages in cell development, Table 1 was prepared from our results. The estimates were obtained by combining the qualitative description of cell types present in each of the twelve stages of the cycle of the seminiferous epithelium[9] with a frequency distribution based on a sample of 3,000 randomly selected tubule cross-sections of normal mice[8].

Table 1. Timing of Cell Development in Spermatogenesis of the Mouse (based on Refs. 8 and 9)

Stage	Duration (hr.)	Interval to release of mature sperm from tubule (days)	
		Minimum	Maximum
Spermatogonia:			
Type *A*	Always present	33·5	35·5
Intermediate	27·3	28·8	30·0
Type *B*	29·4	27·6	28·8
Primary spermatocytes:			
Resting (preleptotene)	31·0	26·3	27·6
Leptotene	31·2	25·0	26·3
Zygotene	37·5	23·4	25·0
Pachytene	175·3	16·1	23·4
Diplotene	21·4	15·2	16·1
Diakinesis + metaphase I	10·4	14·8	15·2
Secondary spermatocytes	10·4	14·4	14·8
Spermatids	229·2	0·0	14·4

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We wish to comment on Dr. Oakberg's criticism of our communication[1]. We stated there that the transcription of frequency of tubule stages from rat to mouse could provide only "approximate intervals". However, when our communication was written, Oakberg's paper on the timing of spermatogenic stages in the mouse[8] was not available to us, and we had to extrapolate from the rat[3] on the assumption that spermatogenesis in these species was similar: this we clearly stated[1]. We realized, therefore, that only "reasonable agreement" could be expected between the cytological and tracer results as we presented them, and that work similar to that of Ortavant in the ram[4] gives a clearer indication of the duration of spermatogenesis[5]. Furthermore, Oakberg has obviously overlooked the assumption, based on the work of Swift[6], that we made in our calculations on the tracer results[1], namely, that preleptotene spermatocytes were initially labelled by adenine.

Using the maximum timing of spermatogenic stages given by Oakberg (preceding communication) and a total spermatogenic cycle of 34·5 days[8], the values in the first column of our Table 1 [1] should be increased by one day for spermatogonia *B* and resting spermatocytes, and decreased from 9 days to 8·2 days for leptotene (from the estimates of Leblond and Clermont[3] we previously used the equivalent of the maximum timing[1]). The latter correction will reduce the figures in the second column by 0·8 day. The first appearance of spermatids (early spermatids) which is the crucial one for determining the interval of transit through the vasa, and therefore for the sampling of the spermatogenic stages at insemination, remains 20 days as given. Our estimates[1] appear, therefore, to be "without serious error". If the stages responsible for oligospermia and aspermia are recalculated using the time ranges proposed by Oakberg the results remain identical with our original calculations[1]. Furthermore, our Table 2 (of the approximate stages of spermatogenesis sampled in ejaculated spermatozoa) remains as given but for the substitution of spermatogonia *A* for intermediate

spermatogonia at centre of week 6. It must be stressed that these calculations are based on the average rate of spermatogenesis[5,7] (see below).

We would like to make two further remarks on Dr. Oakberg's present communication. First, the tracer results are not quite in agreement with the cytological results as he claims. The front of labelled deoxyribonucleic acid shows a precedence of about four days, already apparent at the earliest spermatid stages and preserved until ejaculation, over the cytological timing (unpublished work). The latter is an average timing whereas the tracer observations detect the faster rate of development of certain spermatogenic cells. This situation is evinced in the mixing of stages and in the character of the cytological scores commented on by Oakberg[2] (p. 514). Lastly, we can extend Oakberg's statement that there is no delay during meiosis due to irradiation. The interval from zygotene to ejaculation is not increased after 200 r. of X-rays (unpublished work). This also indicates that the vasa are not damaged by this dose, at least so far as progression of spermatozoa is concerned, and that there is no significant *vis a tergo* from the testis.

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Primary Sex Ratio of Fowl

The only information concerning the primary sex ratio of birds, based on acceptable criteria, is to be found in a publication by Hays which relates to Rhode Island Red fowl[1]. Hays's results give the sexes in the progenies of 39 hens which in the course of a ten-year period had shown 100 per cent fertility and 100 per cent hatchability of their eggs during the two-months hatching season of one of these years. The 39 hens in question had a total of 931 offspring: 61 chicks were lost before the sex could be ascertained; among the remaining 870 chicks, 432 were males and 438 were females. These results clearly pointed to equality of the sexes as determined at fertilization. Yet, Hays suggested (see below), that significant differences may have existed between individual hens in the sex ratios of their offspring.

It seemed desirable, therefore, to collect additional evidence bearing on both problems, namely, the primary sex ratio and its variance between groups of progenies. Such results are here presented for White Leghorn and for Black Minorca fowl. The conditions laid down for inclusion of results in our tabulations were as follows: each hen must have laid a minimum of three eggs a week for at least three consecutive weeks; all of the eggs must have been fertile and all embryos must have survived the eighteenth day of incubation. Sex of the hatched chicks and of the embryos that had died after the eighteenth day was ascertained by dissection. There were four pen matings of each of the two breeds.

Table 1. Sex Records of White Leghorn Embryos and Chicks

Pen	No. of progenies	Embryos and chicks		
		Total	♂♂	♀♀
23	18	493	259	234
24	16	502	249	253
25	16	581	297	284
26	15	476	246	230
Total	65	2,052	1,051	1,001

Table 2. Sex Records of Black Minorca Embryos and Chicks

Pen	No. of progenies	Embryos and chicks		
		Total	♂♂	♀♀
19	17	486	239	247
20	10	235	106	129
21	15	421	214	207
22	16	362	173	189
Total	58	1,504	732	772

The sex ratio data, summarized by pens, are given in Tables 1 and 2. There were 65 progenies of White Leghorns with a total of 2,052 embryos and chicks. Among these were 1,051 males and 1,001 females or $51{\cdot}2 \pm 1{\cdot}12$ per cent males. For Black Minorca fowl we had 58 progenies containing a total of 1,504 embryos and chicks; among these were 732 males and 772 females or $48{\cdot}7 \pm 1{\cdot}29$ per cent males. It is clear that for both breeds, as was true for the results on Rhode Island Red fowl obtained by Hays, the primary sex ratio does not deviate significantly from equality.

In the presentation of his results, Hays gave the sex records of the progenies of those eleven hens in which no chicks had been lost (his Table 2). Without analysing these results statistically, he concluded "that great variability occurs in the primary sex ratio between different families". Hays continued: "This variability may be ultimately traced to gene differences. It is not at all unlikely that sex in domestic chickens may depend upon many genes and that many of these are located in the autosomes". What is the evidence? We have determined for each of our eight pen matings, and also for the entire groups of White Leghorn and Black Minorca fowl, whether significant heterogeneity in the sex ratio of their progenies existed between hens. The values for χ^2, degrees of freedom and probability are summarized in Table 3. The results are entirely negative, that is, there is no evidence for or suggestion of

Table 3. Significance of Deviations from Equality of the Two Sexes between Progenies of Individual Hens

Pen	χ^2	D.f.	P (about)
19	11·81	16	0·75
20	8·79	9	0·46
21	15·61	14	0·45
22	5·11	15	>0·99
All Minorca	43·43	57	>0·50
23	21·30	17	0·25
24	15·08	15	0·40
25	12·47	15	0·60
26	12·40	14	0·60
All Leghorn	62·08	64	>0·50
Hays's Rhode Island Red (his Table 2)	11·66	10	0·30

heterogeneity. Included in Table 3 is also a χ^2 analysis of the data presented by Hays in his Table 2, and this again failed to produce any proof for independent variation between hens in the sex ratio of their progenies. It may be concluded, therefore, from Hays's results as well as from our own, that in fowl equal numbers of males and females are determined at fertilization. There is no evidence whatever for autosomal sex-determining genes or for variations in sex ratio determined by such autosomal genes or by any other agency. Coles[2] has recently published results for a flock of White Leghorn fowl which, he believed, demonstrated a significant deficiency of males in the primary sex ratio of the progenies. The statistical evaluation of his data was made on the unproved assumption that embryonic mortality prior to the tenth day of incubation affects the two sexes in equal proportions. Moreover, the possible significance of selective mortality in unrecognized early stages of segmentation (likely to be classified as 'infertile') was not taken into account. But for a critical evaluation of the primary sex ratio, data should not be accepted in which 'infertility' and early mortality play an unknown part—unless it can, indeed, be shown that on the most unfavourable assumption, namely, all unknowns being of the sex that is deficient in numbers, the deviation of the primary sex ratio from equality remains significant.

Weir[3] and McWhirter[4] have published evidence suggesting that in mammals, with male heterogamety, the primary sex ratio can be modified by specific physiological conditions of the male parent (blood *p*H), and that these conditions can be affected by selection. In animals with female heterogamety, such as birds, it is less likely that similar attempts (though positive results by dietary means have been claimed[5]) will be successful; not, in any event, without a corresponding loss in fecundity or 'fertility'.

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Alimentary Lipæmia and Resistance to Altitude Anoxia

Several recent clinical studies[1] have pointed out important relationships between alimentary lipæmia and the function of the circulatory system after a single large fat meal. The occurrence of typical attacks of angina pectoris especially was observed at the peak of the serum opalescence, accompanied by changes in the electrocardiogram and balistocardiogram. According to various authors many factors participate in these disturbances: increased blood sedimentation-rate and viscosity, decreased fibrinolysis, agglutination of erythrocytes in the blood vessels, and other factors. The possible effect of a relative lack of oxygen in the tissues when the organism is suddenly overloaded with fat was not taken into account. Therefore an experimental study of the effect of alimentary lipæmia upon the resistance of the animal organism to lack of oxygen was undertaken, as the first step towards solving this problem.

The experiments were carried out on *H*-mice of both sexes. Hyperlipæmia was produced by olive

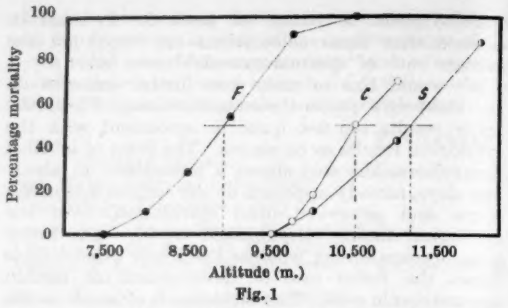

Fig. 1

oil (0·4 ml./20 gm. body-weight) which was given by means of a metal gastric tube, and the resistance of the animals to altitude anoxia was measured first by determining the mean lethal altitude[2] and then by observing the average survival time at a constant simulated altitude.

The mean lethal altitude was studied in three groups of forty mice. Four hours after the administration of fat, that is, at the time when the maximum lipæmia might be expected, small groups, with five in each, of control and fat-treated animals were exposed to simulated altitude of 7,500 m.–11,000 m. The maximum altitude was reached in 1 min., held for another minute and then followed a gradual descent. The percentage mortality in the different altitudes was expressed according to Behrens, the significance between the mean lethal altitudes in the different groups being determined by means of a graphical modification of the probit analysis according to Lichtfield and Wilcoxon[3]. The difference of mean lethal altitude of the control group (*C*) and the fat-treated group is highly significant and amounts to about 1,500 m.

There is no significant difference between the control (*S*), which received an isocaloric amount of starch by means of the gastric tube, when compared to the control (*C*).

The average survival time at the constant altitudes of 11,000, 10,000 or 9,000 m. above sea-level was determined by the last breath (Fig. 2). At the altitude of 11,000 m., 4 hr. after consumption of the

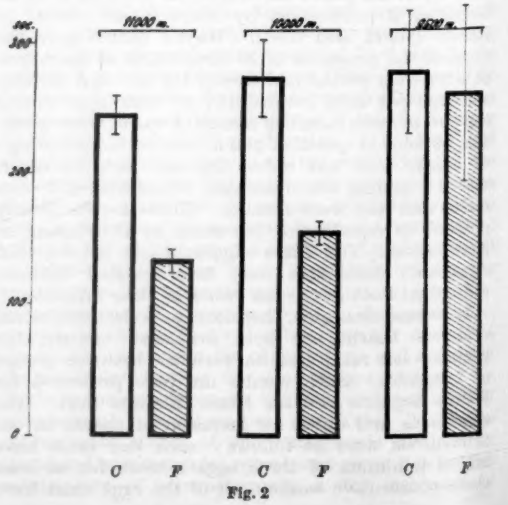

Fig. 2

olive oil it was 133·5 ± 10·2 sec. (variation coefficient 7·5 per cent), in the control group 245·0 ± 7·3 sec. (variation coefficient 7·3 per cent), that is, 65 per cent longer than in the fat-treated group. The time of survival at the altitude of 10,000 m., again 4 hr. after the ingestion of fat, was 156·0 ± 11 sec. (variation coefficient 22·3 per cent); in the control group 272·8 ± 30 sec. (variation coefficient 33·3 per cent), that is, 60 per cent longer. The difference is highly significant at the 1 per cent level. The significance of the difference of survival times disappears at an altitude of 9,500 m., 24 hr. after the administration of oil or starch.

The results presented in this report show a decreased tolerance of anoxia in mice 4 hr. after the application of a single dose of olive oil. Furthermore, they provide evidence for the participation of the above-mentioned relative hypoxia of the tissues after a single load of fat in the different unfavourable changes of the circulatory system due to an increased demand of oxygen in the tissues or due to an altered mechanism of oxygen transport. The different factors are fully analysed in further experiments which will be published in detail elsewhere.

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Lævan-forming Halophilic Bacteria

NON-HALOPHILIC bacteria which are able to form lævan from sucrose have been described within several genera, for example, *Bacillus*[1], *Pseudomonas* and *Xanthomonas*[2], *Streptococcus*[3], *Aerobacter*[4], as well as *Corynebacterium*[5]. However, lævan-forming bacteria occurring among the halophiles offer special interest from the enzymological point of view and, in addition, are of considerable economic importance.

Strains of bacteria which produce a viscous slime on nutrient agar containing six per cent sucrose and eight per cent sodium chloride were isolated from 'ropy' herring brine. These bacteria are non-spore-forming, non-motile, Gram-negative rods. They are obligate halophiles of the moderate type, showing maximal growth at 1–2 *M* sodium chloride, within the temperature range 20–30° C., and around *p*H 7. Neither acid nor gas is formed from carbohydrates. The bacteria are aerobic, but are able to grow under anærobic conditions in the presence of nitrate which is reduced to nitrite and gas. Provisionally, they have been classified within the genus *Achromobacter*.

Neither lithium nor potassium can be substituted for the sodium ions, but bromide, sulphate and phosphate may partially replace the chloride ions.

The bacteria may be grown in synthetic media, supplemented with thiamine. Glutamic and aspartic acids are utilized as sole sources of carbon, energy and nitrogen. In the presence of ammonium salts, pyruvic, citric, succinic, fumaric and malic acids as well as α-alanine support growth. No other amino-acid tested could be used as sole carbon source, in spite of the fact that the readily water-soluble amino-acids are all oxidized rapidly by washed cells in the Warburg apparatus. None of the carbohydrates tested, for example, arabinose, xylose, glucose, mannose, galactose, fructose, sucrose, maltose, lactose, raffinose and starch, can be used as carbon and energy source; nor are these substances oxidized in the Warburg apparatus. Thus, these bacteria do not attack carbohydrates, with the one exception that sucrose is transformed to a slime if the bacteria are at the same time provided with some source of carbon and energy which they can utilize, for example, certain amino-acids, pyruvic acid, or intermediates of the tricarboxylic acid cycle.

The slime formed from sucrose was precipitated by the addition of two volumes of 96 per cent ethanol. It was found to contain less than 0·05 per cent nitrogen. After hydrolysis[6] by heating in 0·1 *N* oxalic acid for 45 minutes at 70° C., neutralization with calcium carbonate and centrifuging, the hydrolysate gave only one spot on the paper chromatogram. By means of its R_F value and colour reaction with naphthoresorcinol, this spot was identified as fructose. The results indicate that the slime substance is a polysaccharide of the lævan type and the enzyme active in its formation a lævansucrase.

For the study of the enzyme activity, acetone-dried preparations of the bacteria were used. The relative increase of viscosity, caused by the acetone-dried cells in a solution containing 0·08 *M* sucrose, 8 per cent sodium chloride, and 0·1 *M* phosphate buffer, *p*H 7·0, was taken as a measure of the enzyme activity. The lævansucrase was found to be constitutive and bound to the cells, showing little or no activity in solutions without added sodium chloride, with maximal activity in the range 1–3 *M*. Very low activities were obtained when the bacteria were washed several times with lithium or potassium chloride solutions before the acetone treatment, and determinations of the activity were made in solutions containing either of these chlorides instead of sodium chloride. It appears that the lævansucrase of these bacteria is specifically activated by sodium ions.

Whereas non-halophilic lævan-forming bacteria form slime from raffinose as well as from sucrose, the bacteria studied in the present work are only able to use sucrose as substrate. Other sugars, added to the sucrose-containing solution, inhibit the slime formation to varying degrees, the strongest effect being obtained with lactose.

Although the lævansucrase is a constitutive enzyme, the growth conditions of the bacteria seem to affect the amount of enzyme formed or its activity. From bacteria grown in aerated media or in the presence of nitrate, acetone-dried preparations of much higher activity were obtained than from cells grown under limited oxygen supply.

A detailed report of the results will be given elsewhere.

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Respiratory Metabolism of Aerated Potato Disks

Research in several laboratories has clearly demonstrated that aerated potato disks develop an increased capacity for uptake of oxygen[1–7]. This additional respiratory capacity is not increased by 2,4-dinitrophenol[7] and is relatively insensitive to inhibition by cyanide[6] and carbon monoxide[5,6]. However, cyanide[8], low temperature (0–5° C.)[7] or absence of oxygen at normal temperature[5] will prevent the development of the increased respiratory capacity.

In view of these observations, it became of interest to us to learn whether the development of increased respiratory capacity requires the synthesis of new protein and whether the increased oxygen uptake is coupled to phosphorylation to give an increased work capacity. In our experiments (Table 1) the presence of the protein synthesis inhibitor, chloramphenicol, during the 24-hr. aeration of the potato disks prevented increase in respiratory capacity. Because the presence of chloramphenicol during the measurement of uptake of oxygen has little effect on the respiration of either fresh or aerated disks, it can be concluded that protein synthesis is a necessary part of the development of an increased capacity for uptake of oxygen.

Table 1. The Effect of Chloramphenicol on the Development of an Increased Respiratory Capacity by Aerated Potato Disks. Oxygen uptake (μl. O_2/500 mgm./hr.)

Fresh control	Fresh + chloramphenicol	Inhibition (per cent)	Aerated control	Aerated in the presence of chloramphenicol*	Inhibition (per cent)
24	19	25	105	33	69
24	25	−4	50	16	68
32	29	9	101	55	46
Av. 27	24	10	85	35	61

* Potato disks were aerated in the presence of 1 mgm./ml. chloramphenicol for 24 hr.

Each Warburg flask contained: 0·01 *M* phosphate, *p*H 6·9, 500 mgm. potato disks (1 cm. × 1 mm.), 3×10^{-4} *M* hydrogen cyanide or 1 mgm./ml. chloramphenicol, 20 per cent potassium hydroxide in the centre well. Incubation temperature, 30° C.

The phosphorylative capacity of the potato disks was measured by determining the extent of incorporation of phosphorus-32 into organic phosphate esters during the measurement of uptake of oxygen. Results obtained in this way indicate that the increment of respiratory capacity is coupled to phosphorylation (Table 2). The incorporation of phosphorus-32 into the aerated disks is not as sensitive to inhibition by cyanide as that of fresh disks. However, the phosphorylation of aerated disks is inhibited by the same levels of dinitrophenol required to inhibit the phosphorylation of fresh disks.

Table 2. Effect of Cyanide on the Phosphorylation Capacity of Fresh and Aerated Potato Disks

Incorporation of phosphorus-32 into organic esters. (Per cent of total counts in the cells)

Fresh control	Fresh + HCN	Inhibition (per cent)	Aerated control	Aerated +HCN	Inhibition (per cent)
32·6	13·7	58	23·6	30·1	−27·5
12·6	4·2	67	27·6	24·5	11·2
23·9	8·1	66	32·7	25·6	21·7
—	—	—	23·5	18·3	22·1
—	—	—	19·9	25·0	−25·6
Av. 23·0	8·7	64	25·5	24·7	0·4

Incubation with phosphorus-32 was conducted in a Warburg flask during measurements of oxygen uptake. The flasks contained 0·01 *M* phosphate buffer, 500 mgm. (fresh weight potato disks), 3×10^{-4} hydrogen cyanide and 20 per cent potassium hydroxide in the centre well. Incubation was at 30° C. for 3 hr.

These results lead us to the conclusion that the increased respiration of aerated potato disks is mediated by enzymes which are synthesized during the aeration period. Further, it appears that this additional electron transport to oxygen is coupled to phosphorylation because the phosphorylation observed in a fixed incubation time is not sensitive to a level of cyanide sufficient to inhibit 64 per cent of the phosphorylation of fresh disks. If the additional respiration were not coupled to phosphorylation, then the phosphorylation after 24-hr. aeration should still be sensitive to cyanide inhibition.

The results reported here can be accounted for by the hypothesis that cytochrome oxidase is a limiting factor in the respiration of fresh potato disks; and that on aeration, there is a net synthesis of an excess of cytochrome oxidase so that this cyanide-sensitive step is no longer limiting.

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Ion Permeability of the Plasmalemma of the Plant Cell

Walker[1] has suggested that for *Nitella* there is evidence for a layer on the outside of the cytoplasm, a plasmalemma, which offers considerable resistance to the passage of ions. In support of this suggestion he advances two pieces of evidence—the bulk of the high d.c. resistance across the cytoplasmic layer from vacuole to outside solution of chloride lies in the cytoplasm and not in the tonoplast, and secondly, that the equilibrium concentration of calcium ions in the cytoplasm calculated from the potential difference is absurdly high.

If the tonoplast is practically impermeable to cations, then the conductivity of the cytoplasm and tonoplast will depend on the concentration and mobility of anions in these phases. If they are similar for both phases, then the bulk of the resistance will reside in the cytoplasm because of its much greater thickness. The average resistance of 6,000 ohm sq. cm. with a thickness of 10μ would be appropriate for a concentration of chlorine ion in the cytoplasm of 2·6 μequiv./l. This is the equilibrium concentration if the external solution has a concentration of 1·5 m.equiv./l. and a potential difference relative to the cytoplasm of 160 mV. If the external cation were univalent then the concentration of non-diffusible anion would be 0·87 equiv./l. The external concentration and that of non-diffusible anion would be smaller if the potential difference were less. The concentrations used ranged from 0·05 to 1·0 m.equiv., but the values for the potential difference with these solutions are not given.

The calculation of calcium ions in the cytoplasm is valid if the potential difference of − 160 mV. is the correct value for the cells in pond water (potassium, 0·03; sodium, 0·5; and calcium, 0·5 m.equiv.) and the estimation of calcium refers to the free ion. It is worth noting that Walker[2] reports − 160 mV. for cells in unspecified volumes of 0·0001 *M* potassium chloride and −123 mV. when the concentration was changed to 0·001 *M*. Unfiltered pond water may contain solid calcium carbonate. In any event the calculation, if based on firm premises, cannot tell us anything about mode of entrance of calcium, whether as ions or combined with carrier molecules, as Walker suggests; it can only tell us whether or not the cytoplasm and external solution are in equilibrium as regards calcium.

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Control of Witchweed, *Striga hermonthica* Benth., in the Sudan Gezira

Recent work[1] has shown that the phanerogamic root parasite *Striga hermonthica* Benth. (witchweed), which causes considerable crop losses to sorghum (*Sorghum vulgare* Pers.) in the Sudan and elsewhere, can be controlled by spraying the young crop with hormone weed-killers of 2,4-D type two to three weeks after sowing. Although such measures often result in substantial increases in yield, there are several difficulties which at present preclude their general adoption in the Sudan Gezira. One is the extreme sensitivity of certain crops, notably cotton, to even minute traces of hormone weed-killers, together with the fact that such spraying has to be carried out at about the time of cotton sowing in the Gezira. Furthermore, spraying must be carefully timed and performed to avoid injuring the young sorghum plants, and involves the use of relatively costly and complicated spraying apparatus with which most Gezira cultivators are unfamiliar—the initial cost and subsequent maintenance of such apparatus discourage many cultivators from using this method of witchweed control.

An investigation of simpler methods of application was carried out on ridge-irrigated sorghum sown on July 14, 1956, in a plot with high natural witchweed infestation, and the results are given in Table 1. The fine spray was from a knapsack sprayer using some 92 gallons of weed-killer solution per acre. Sprinkler application was from an ordinary watering-can with a rather coarse rose, using about 184 gallons/acre. Jet application was from a watering-can delivering a narrow jet of solution, the open end of the spout being covered with a simple metal cap having a circular aperture, ¼ in. in diameter. This adaptation worked efficiently, did not become blocked and allowed application of the weed-killer solution at the rate of 46 gallons/acre. In all treatments except control, 1 lb. of 80 per cent 2,4-dichlorophenoxyacetic acid per acre was applied on July 31, seventeen days after sowing.

All ridge applications (2–5, 7–9) greatly reduced early witchweed attack but not so the two furrow applications (6, 10); two months after sowing, witchweed infections, as judged by percentage infected plant holes, were about the same in all treatments. Yields of grain varied considerably within replicates of the same treatment, partly due to damage by birds and dura midge (*Contarinia sorghicola*), and although treatments with heavy early witchweed attack tended to yield less grain, the differences were not quite significant at the *P* 0·05 level. Thus in the ten control (untreated) replicates yields of grain ranged from one to nearly six ardeb/acre, and plant holes infected by witchweed on September 5 ranged from 40·8–86·5 per cent. Analysis (see Table 2) of the results from these ten untreated replicates showed highly significant negative correlations between yield (grain and straw) and the percentage of infected holes on August 22 and on September 5, but not at later dates, when infection had increased to about the same level in all ten subplots.

Table 1

Method of application	Percentage plant holes attacked by witchweed Aug. 22	Sept. 5	Sept. 19	Oct. 3	Yield/acre Grain (ardebs)	Straw (tons)
1 Control, untreated	32·9	71·4	97·6	98·8	3·020	1·309
2 Spray along ridges, continuous	2·5	27·0	82·4	93·0	5·030	1·979
Sprinkler along ridges:						
3 Continuous	2·6	21·0	91·2	93·2	5·080	2·080
4 Between plant holes	9·1	30·5	94·1	96·0	4·111	1·870
5 Over plant holes	3·1	32·3	85·0	94·7	4·404	2·050
Sprinkler along furrows:						
6 Continuous	22·5	46·1	93·2	96·2	4·171	1·585
Jet along ridges:						
7 Continuous	2·1	26·1	88·1	94·7	5·595	2·266
8 Between plant holes	9·4	37·3	91·5	95·2	5·181	2·289
9 Over plant holes	4·8	29·1	92·9	96·4	4·666	1·907
Jet along furrows:						
10 Continuous	36·7	61·2	95·1	96·8	4·167	1·578
Minimum significant difference $P = 0·05$					not sig.	0·474
$P = 0·01$						0·628

1 ardeb ≃ 332·6 lb.

Table 2. Correlation Coefficient (r and t) between Yields of Grain and Straw and Percentage Infected Holes on August 22 and September 5

	At $P = 0·05$, $t = 2·306$
	At $P = 0·01$, $t = 3·355$
Aug. 22:	Grain yield, $r = -0·844$, $t = 5·289$
	Straw yield, $r = -0·825$, $t = 4·128$
Sept. 5:	Grain yield, $r = -0·746$, $t = 3·168$
	Straw yield, $r = -0·897$, $t = 5·740$

Straw yields were more consistent and were significantly increased by all treatments except the two furrow applications. Ridge application from watering-can, whether by sprinkler or jet, was as effective as spraying, and this method of application should reduce the cost and increase the simplicity of witchweed control. Jet application of the weed-killer solution would also lessen the danger of spray drift to nearby crops.

This control method delays witchweed attack by destroying the first flush of germinating *Striga* seedlings, but the weed-killer does not persist in the soil sufficiently long to destroy seedlings appearing later; that is to say, it reduces but does not eliminate the parasite. It is hoped to investigate whether pre-sowing application of persistent non-hormone weed-

killers of the substituted urea type (CMU, DMU) will destroy germinating witchweed seedlings without adversely affecting the sorghum crop; the witchweed problem would be greatly simplified if effective control could be obtained by application of such compounds during the dry intercrop months before sorghum is sown.

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May 11.

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[1] Jones, K. W., *Empire J. Exp. Agric.*, **20**, 98 (1952).

'Compensatory Hyper-regeneration' in the Antennæ of Hemiptera

It has been observed by several authors[1] that antennæ of various Hemiptera, especially Lygaeidae, occasionally exhibit an abnormality in which the number of antennal segments is reduced but at the same time the length of the remaining ones is increased, as if the loss of one segment were compensated by an exaggerated growth of the rest. I have presented evidence[2] indicating that such cases in the Pentatomid bug *Raphigaster nebulosa* must be due to an incomplete regeneration after the loss of a normal antenna during nymphal stages, but so far neither experimental evidence for this nor a satisfactory explanation of the 'compensatory' nature of the abnormalities has been available. (Dr. H. Ruckes, of the American Museum of Natural History, New York, tells me that he has produced such 'compensatory hyper-regeneration' experimentally on antennæ of the Pentatomid bug *Euchistus variolarius*, but his findings have not been published.)

Experiments with the milkweed bug *Oncopeltus fasciatus* have now furnished direct proof that antennæ, showing the 'compensatory' phenomenon, that is, having fewer but larger segments than normal antennæ, can be produced experimentally by removing the original antennæ in early nymphal stages and allowing the organ to regenerate. The best results were obtained when the antennæ were amputated (on one side, so that the opposite side could serve as control) in first or second instar nymphs, that is, within six days after hatching at about 25° C. The antennæ were amputated either near the basal segment, removing three segments and leaving the basal one intact, or near the articulation of the second and third segments, removing the two terminal segments. In place of the amputated segments the regenerates had always one segment less than the normal antenna. If three segments were amputated, the regenerate had only two in their place; if two were removed, they were replaced by one only. The regenerated antenna as a whole never reached the size of the normal one, but its relative size in comparison to the normal varied a great deal, obviously due to differences in the physiological conditions of the insects during the process of regeneration. The length of the individual segments of the regenerates also often remained below normal, or just reached the normal size; but in about half the cases regenerated segments have appeared which were conspicuously longer than any of the segments of a normal antenna, just as in the cases found in Nature (Fig. 1,*a*). In addition, in most

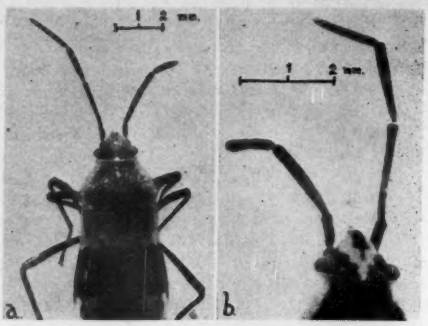

Fig. 1. *Oncopeltus fasciatus* adults, with regenerated antennæ: (*a*) right antenna was removed at the base of the second segment in the first nymphal stage—note the abnormally long second segment of the regenerate; (*b*) left antenna was amputated in the same place, same stage. Segments of the regenerate are shorter but thicker than normal

cases the regenerated segments, even the ones which were shorter than the normals, were considerably thicker and 'chubbier' than those of a normal antenna (Fig. 1,*b*). They often gave the same impression, when compared with normal antennæ, as that given by polyploid leaves or fruits of a plant when compared with the diploid organs (cf. Blakeslee[3]).

An attractive explanation of the cause of the oversize dimensions of the regenerated antennal segments offers itself, since it is known that in various post-embryonic developmental stages of insects chromosome duplications occur regularly in somatic cells without nuclear division[4] and this phenomenon, termed endomitosis, is particularly widespread in Hemiptera[5]. It seems that many organs of these hemimetabolous insects grow from nymphal instar to nymphal instar not by a multiplication of the number of the constituent cells but by a systematic increase in the size of the cells, due to repeated endomitotic polyploidization of the nuclei.

Studies in progress in this Laboratory on the cytology of *Lygaeus* and *Oncopeltus* under Prof. C. A. Berger (unpublished work by C. M. John and B. Sparano) indicate that practically all somatic tissues of these insects undergo progressive polyploidization during nymphal stages. It is therefore almost certain that the cells which form the regeneration blastema on the stump of an amputated antenna have a higher number of chromosome complements (and are consequently larger) than those which formed the anlage of the original antenna during embryogenesis. The result seems to be the observed increase in the dimensions of the regenerated structures when compared with the original ones. Whether the reduction in the number of antennal segments in the regenerates is a consequence of the polyploidy of the cells of the regeneration blastema or an independent phenomenon cannot be decided on the basis of the facts presented here. (Imperfect regeneration is widespread even in forms where somatic polyploidy does not occur.) But it may well be that increasing polyploidy affects adversely the capacity of the tissues to differentiate. It was observed, for example, that amputation of antennæ in late nymphal stages, when polyploidy reaches its maximum, no longer produces regeneration, but the stumps seem to be noticeably 'swollen', indicating that cell divisions have still occurred. Further studies in this direction, as well as in order to check this tentative explanation

of the 'compensatory hyperregeneration' of Hemipteran antennæ, are in progress.

ALEXANDER WOLSKY

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June 14.

[1] Esaki, T., *Zeitschr. Wiss. Insektenbiol.*, **20**, 1 (1925). Müller, G., *ibid.*, **21**, 51 (1926).
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Lamprey Distribution in Streams and Rivers

IT has long been known that there is a close relation between gradients of rivers and their living population[1–5]. Many accounts have stressed the way in which these populations (especially fish) tend to move up or down a river, depending on its water-level and rate of flow. I have noticed that lampreys and their larvæ do not seem to do this. Apart from those instances where, during severe drought or drought followed by flooding, ammocoete beds dry out or are washed away, such beds and the ammocoetes in them usually remain where they are whatever the state of the river.

My own observations[6] point to two conclusions. (1) The building up of an ammocoete bed is a function of the gradient of a river and, once made, the bed will withstand severe changes in water-level and flow providing it does not dry out. (2) The ammocoetes themselves, by living in the ammocoete bed, are in fact not in the ecological environment of the main stream but in a micro-environment of their own.

Lampreys, like fish, are very sensitive to increases in the temperature and carbon dioxide content of water. Changes of this sort are less likely to occur in reaches of a river where the gradient exceeds 10 ft. per mile[5,7] and distribution records of the occurrence of lampreys, particularly the brook lamprey (*Lampetra planeri* Bloch), which I have collected over a number of years indicate a broad correlation between distribution of lampreys and gradients of stream of between 10 ft. per mile and 30 ft. per mile. In addition, however, I have found certain regular variations within these limits which require further investigation.

It is the purpose of this communication to seek the help of all those who know of stream or river localities in which lampreys occur, so as to increase the amount of information to a level where it can be analysed statistically.

The information sought is as follows: (1) Any evidence of the existence, or former existence, of lampreys or ammocoetes of any species in a particular stream or river. (2) Identification of the species, if possible. (3) An accurate description, preferably by map reference, of the locality. In Britain, 1-in. Ordnance Survey (and edition) is sufficient. (4) Date on which specimen was observed. (5) Any weather observation made at the time.

I shall be grateful to receive even single records. Such information from any part of the world will be of value as I have access to large-scale maps here in London which will enable me to determine the general geographical features of any locality.

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June 3.

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Occurrence of *Elminius modestus* Darwin in Ireland

THE appearance, and subsequent spread, of the Australasian barnacle *Elminius modestus* Darwin in British and north European waters is well known[1]; but, hitherto, it has not been recorded in Ireland.

On September 12, six small specimens of *E. modestus* were found at Tralispean and on September 15, four more were discovered on the east side of the Coosh, near Lough Ine in south-west County Cork[2]. Both are sheltered localities. The specimens were found near low water, and the carino-rostral diameter of the largest specimen was 5 mm.

An immediate study of the general distribution of *E. modestus* in Ireland should establish its point of entry.

D. M. BEARD

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University of Bristol.
Oct. 15.

[1] Bishop, M. W. H., *Nature*, **159**, 501 (1947). Stubbings, H. G., *Nature*, **166**, 277 (1950). Bishop, M. W. H., *Nature*, **173**, 1145 (1954). Crisp, D. J., and Chipperfield, P. N. J., *Nature*, **161**, 64 (1948). Connell, J. H., *Nature*, **175**, 954 (1955). Boschma, H., *Nature*, **161**, 403 (1948). Bishop, M. W. H., *Nature*, **167**, 531 (1951).
[2] Renouf, L. P. W., *J. Ecol.*, **19**, 410 (1931).

Some Further Visual Phenomena associated with Regular Patterned Stimulation

IN a recent article[1] I described some striking effects of visual stimulation by regular patterns. The principal feature of these is the appearance of what may be called a 'complementary pattern' the main outlines of which run roughly at right-angles to those of the stimulus-pattern. A 'ray' pattern of radial lines, for example, produces an after-impression of wavy lines moving in concentric circles; a pattern of concentric circles produces an after-image of wavy radial streamers. These complementary patterns may also be evoked continuously in stroboscopic light, or in a background of visual 'noise' (on a television screen) viewed through a transparency of the stimulus pattern.

Since the article was written a number of related effects have been discovered, two of which appear to be of special interest. The first is observed when a source of visual 'noise' is presented after a ten-second viewing of the stimulus pattern in normal light. The spots of light on the screen, which normally suggest an incoherent 'Brownian motion', are for a a few seconds organized into a vigorous scurry of apparent movement roughly along the lines of the

complementary pattern. This after-effect shows little transfer (when the stimulus is presented to one eye and the screen is viewed afterwards by the other). It has been found, however, that if one eye views the stimulus pattern and the other simultaneously views the screen, some similar but less-violent motion of the spots on the screen can be seen continuously.

It has been found that this phenomenon, as well as those described earlier, is unaffected when the stimulus presented is stabilized against eye-movement. This has been done by mounting a photographic reduction of the pattern on a stalk 1·5 cm. long attached to a contact lens of + 60 dioptres power. (A similar method of stabilization has been used independently by Prof. R. W. Ditchburn of Reading in another connexion (personal communication).) The stimulus-pattern 'fades' irregularly, as expected, but even when it has faded the other eye can detect the complementary motion in the spots of 'noise' on the screen.

This evidence of limited transfer complicates an already puzzling picture, and suggests that in these phenomena we may be dealing not with a single localized activity but with an activity to be expected in the highly interconnected visual network at several, if not all, levels from retina to cortex.

The second effect to be reported is seen with a stimulus pattern consisting of concentric rings of increasing thickness (Fig. 1). Viewed monocularly in bright light, this evokes a radial complementary image which is seen in apparent rivalry with it. If now the stimulus pattern is moved slightly towards or away from the subject, the complementary image is observed to contract or expand rapidly, providing a strikingly sensitive indication of motion in depth. The apparent inference is that the elements the activity of which generates the complementary image are highly sensitive to the spacing of the stimulus-contours. The exaggerated sensitivity of the complementary image could then have somewhat the same explanation as the great sensitivity of moiré patterns to relative movement. An important observation, however, is that the phenomenon does not require central fixation. The pattern may be freely explored with eye-movements without disruption of the complementary image. Any explanation based only on the central symmetry of the retinal receptor-pattern would thus seem to be ruled out.

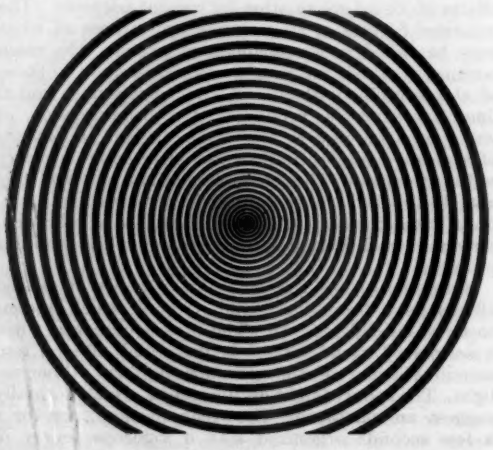

Fig. 1

D. M. MacKay

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Oct. 12.

[1] MacKay, D. M., *Nature*, 180, 849 (1957).

Lord Cherwell

There is little that need be added to the excellent obituary notice of Lord Cherwell in *Nature* of September 21, p. 579, but I should like to comment on the reference to the work in the Clarendon Laboratories in the 'twenties. It is true that the work was diverse, but any one of the problems being studied might have flared up into a whole school of research, which is indeed what many of them have since done.

Griffith was calculating the electrical conductivity due to electrons and ionized molecules in the upper atmosphere, which might very well have led to the work now associated with Appleton's name; Collie was trying to fix Wilson cloud-chamber tracks in gelatine, anticipating Powell's work at Bristol; I was working on the coherence of radiation at different parts of the wave-front, which is now being investigated by Hanbury-Brown and others. One day Lindemann asked me to apply thermodynamical theorems to chemical reactions at extremely high temperatures, beyond anything then known on Earth. The application to stellar constitution and nuclear explosions would have followed.

Lindemann's uncanny foresight revealed to him the importance of the solution of these problems; but, being himself outstandingly adept with his hands, he was apt to suggest experiments which demanded a technique difficult of attainment. In consequence many of the workers became involved in attempts to construct new types of delicate apparatus, and the solution of the main problem was indefinitely delayed.

H. R. Calvert

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Oct. 3.

Museums in Britain

The article in *Nature* of October 19, p. 769, on this subject reported that several museums must close unless financial assistance is rapidly forthcoming. The Government at present considers that financial aid is a local matter. The Royal Institution of South Wales (founded 1835) in Swansea is in a similar position to some of the museums mentioned, but fortunately local industry has come to its support. An industrial section is being formed within this Museum, members of the local University College are co-operating, and funds have been provided by industry to prevent closure.

R. B. Southall
(Chairman)
Hugh O'Neill
(Secretary)

Industrial Museum of South Wales, Ltd.,
The Royal Institution,
Swansea.

FORTHCOMING EVENTS

*(Meetings marked with an asterisk * are open to the public)*

Monday, November 25

ROYAL GEOGRAPHICAL SOCIETY (at 1 Kensington Gore, London, S.W.7), at 5 p.m.—Mr. R. Mansell Prothero: "Heinrich Barth and the Western Sudan".

UNIVERSITY COLLEGE, LONDON (in the Physiology Theatre, Gower Street, London, W.C.1), at 5 p.m.—Dr. H. Harris: "Human Biochemical Genetics".* (Further lectures on December 2 and 9.)

BRITISH SOCIETY FOR THE HISTORY OF SCIENCE (in the Council Room of the Science Museum, Exhibition Road, South Kensington, London, S.W.7), at 5.30 p.m.—Mr. I. B. Hopley: "Clerk Maxwell's Experiments on Colour Vision".

INSTITUTION OF ELECTRICAL ENGINEERS, RADIO AND TELECOMMUNICATION SECTION (at Savoy Place, London, W.C.2), at 5.30 p.m.—Informal evening on "Problems of Sound and Television Broadcasting Coverage". Talk by Mr. G. Millington.

UNIVERSITY OF LONDON (in the Assembly Hall, Institute of Education, Malet Street, London, W.C.1), at 5.30 p.m.—Mr. N. J. Graves: "Geography".* (Last of a series of lectures on "Contemporary Ideas on Teaching Method".)

Tuesday, November 26

INSTITUTION OF CHEMICAL ENGINEERS (joint meeting with the LOW TEMPERATURE GROUP of the PHYSICAL SOCIETY, at the Royal Institution, Albemarle Street, London, W.1), at 9.30 a.m.—Joint Symposium on "Recent Developments in Industrial Low Temperature Gas Separation".

PARLIAMENTARY AND SCIENTIFIC COMMITTEE, GENERAL COMMITTEE (in Committee Room 12, House of Commons, London, S.W.1), at 5.30 p.m.—Discussion on "Problems of Aircraft Research and Development in Great Britain", opened by Mr. H. G. Nelson, Sir William Farren, F.R.S., and Dr. A. E. Russell.

ROYAL METEOROLOGICAL SOCIETY (in the Conference Hall, County Hall, London, S.E.1), at 5.30 p.m.—Mr. H. H. Lamb: "Weather in the Polar Regions" (Popular Lecture for Sixth-form Scholars).

UNIVERSITY OF LONDON (at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1), at 5.30 p.m.—Dr. G. Gordon: "Central Sensory Representation".* (Twelfth of fifteen lectures on "The Scientific Basis of Medicine" organized by the British Postgraduate Medical Federation. Further lectures on November 28, December 3 and 5.)

Wednesday, November 27

INSTITUTE OF PHYSICS, LONDON AND HOME COUNTIES BRANCH (in the Lecture Theatre of the Royal Institution, 21 Albemarle Street, London, W.1), at 2.30 p.m.—Symposium on "The Design of Physics Research Laboratories".

GEOLOGICAL SOCIETY OF LONDON (at Burlington House, Piccadilly, London, W.1), at 5 p.m.—Mr. S. Marchant and Mr. C. D. G. Black: "The Nature of the Clay Pebble-beds and Associated Rocks of South-West Equador"; Dr. G. P. L. Walker: "The Volcanic Geology of the Reydarfjördur Area, Eastern Iceland".

BRITISH INSTITUTION OF RADIO ENGINEERS (at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1), at 6 p.m.—Annual General Meeting. 7.15 p.m.—Dr. A. van Weel: "Transmission Standards and Signal Distortion in Television and Other Communication Systems".

INSTITUTION OF MECHANICAL ENGINEERS, APPLIED MECHANICS GROUP (at 1 Birdcage Walk, Westminster, London, S.W.1), at 6.45 p.m.—Discussion on "Fretting Fatigue".

ROYAL INSTITUTE OF CHEMISTRY, LONDON SECTION (joint meeting with the SOUTH-WEST ESSEX COLLEGE OF TECHNOLOGY CHEMICAL SOCIETY, at the South-West Essex College of Technology, Forest Road, London, E.17), at 7 p.m.—Dr. J. W. Rodgers: "The Extraction and Uses of Titanium and Zirconium".

BRITISH PSYCHOLOGICAL SOCIETY, MEDICAL SECTION (at the Medical Society of London, 11 Chandos Street, Cavendish Square, London, W.1), at 7.30 p.m.—Prof. Michael Polanyi: "The Structure of the Modern Mind".

ROYAL SOCIETY OF MEDICINE (in the Barnes Hall, 1 Wimpole Street, London, W.1), at 8 p.m.—Lord Adrian, O.M., F.R.S.: "The Analysis of the Nervous System" (First Sherrington Memorial Lecture).

Wednesday, November 27—Thursday, November 28

INSTITUTE OF FUEL (at the Institution of Civil Engineers, Great George Street, London, S.W.1), at 10 a.m. daily—Second Conference on "Pulverized Fuel".*

Thursday, November 28

UNIVERSITY OF LONDON (in the Wright-Fleming Institute Lecture Theatre, St. Mary's Hospital Medical School, Paddington, London, W.12), at 5 p.m.—Prof. G. Mayer (Bordeaux): "Physiological Factors in Implantation of the Egg".

INSTITUTION OF ELECTRICAL ENGINEERS (at Savoy Place, London, W.C.2), at 5.30 p.m.—Mr. W. A. Sharpley and Mr. J. V. Oldfield: "The Digital Computer applied to the Design of Large Power Transformers".

RESEARCH DEFENCE SOCIETY (in the Physiology Lecture Theatre, University College, Gower Street, London, W.C.1), at 5.30 p.m.—The Right Hon. the Lord Cohen of Birkenhead: "Some Reflections on Animal Experiments" (Twenty-sixth Stephen Paget Memorial Lecture).

UNIVERSITY OF LONDON (at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, London, W.C.1), at 5.30 p.m.—Dr. H. J. Taylor: "Physiological Problems Associated with Diving and Underwater Swimming".* (Thirteenth of fifteen lectures on "The Scientific Basis of Medicine" organized by the British Postgraduate Medical Federation. Further lectures on December 3 and 5.)

INSTITUTION OF MECHANICAL ENGINEERS, GRADUATES' SECTION (at 1 Birdcage Walk, Westminster, London, S.W.1), at 6 p.m.—Mr. R. E. Zoller: "Some Aspects of Hinkley Point Project".

INSTITUTION OF ELECTRONICS (in the Assembly Hall of the University of London Institute of Education, Malet Street, London, W.C.1), at 6.30 p.m.—Mr. C. Brown: "The High Fidelity Reproduction of Sound" (Lecture-Demonstration).

Friday, November 29

ROYAL SOCIETY (at Burlington House, Piccadilly, London, W.1), at 10.30 a.m.—Discussion on "Observations of the Russian Artificial Earth Satellite and their Analysis", opened by Prof. H. S. W. Massey, F.R.S.

BRITISH PSYCHOLOGICAL SOCIETY, INDUSTRIAL SECTION (in the Department of Psychology, Birkbeck College, Malet Street, London, W.C.1), at 1 p.m.—Mr. H. C. A. Dale: "Fault-finding: Some Recent Research".

INSTITUTION OF MECHANICAL ENGINEERS (in conjunction with the INDUSTRIAL ADMINISTRATION AND ENGINEERING PRODUCTION GROUP, at 1 Birdcage Walk, Westminster, London, S.W.1), at 6 p.m.—Mr. J. L. Rice, Mr. R. W. Ruddle and Mr. P. A. Russell: "Recent Developments in the Manufacture of Castings".

SOCIETY OF COSMETIC CHEMISTS OF GREAT BRITAIN (at the Royal Society of Arts, John Adam Street, Adelphi, London, W.C.2), at 7.30 p.m.—Dr. V. R. Wheatley: "Chemistry and Biochemistry of Sebum".

ROYAL INSTITUTION (at 21 Albemarle Street, London, W.1), at 9 p.m.—Dr. William Syer Bristowe: "A Smother of Spiders".

Saturday, November 30

BOTANICAL SOCIETY OF THE BRITISH ISLES (in the Lecture Hall of the British Museum (Natural History), Cromwell Road, London, S.W.7), from 2.30 to 5.30 p.m.—Annual Exhibition Meeting.

ROYAL SOCIETY (at Burlington House, Piccadilly, London, W.1), at 2.30 p.m.—Anniversary Meeting.

APPOINTMENTS VACANT

APPLICATIONS are invited for the following appointments on or before the dates mentioned:

ASSISTANT (preferably with a good scientific education) IN THE SCIENCE DEPARTMENT, London Headquarters, for editorial and information duties—The Personnel Department, British Council, 65 Davies Street, London, W.1, quoting D.5 (57) (November 26).

ASSISTANT (Grade B) IN PHYSICS—The Clerk to Governors, Woolwich Polytechnic, London, S.E.18 (November 30).

ASSISTANT LECTURER, Grade B (honours graduate), IN PHYSICS at Brighton Technical College—The Director of Education, Brighton Education Committee, 54 Old Steine, Brighton 1 (November 30).

LECTURER IN THEORETICAL PHYSICS—The Registrar, King's College (University of London), Strand, London, W.C.2 (November 30).

LECTURER or ASSISTANT LECTURER IN APPLIED MATHEMATICS—The Registrar, The University, Sheffield (November 30).

LECTURER (preferably with industrial and/or research experience) IN PHYSICAL CHEMISTRY; an ASSISTANT (Grade B) IN BIOLOGY and an ASSISTANT (Grade B) IN MATHEMATICS—The Principal, Nottingham and District Technical College, Shakespeare Street, Nottingham (November 30).

LECTURER (with an interest in electronics, and preferably a knowledge of experimental stress analysis) IN TEXTILE ENGINEERING—The Registrar, The Manchester College of Science and Technology, Manchester 1 (November 30).

SCIENTIFIC OFFICER, to work at Dunholme Field Station, Lincoln, on fungus and virus diseases of sugar beet—The Secretary, Rothamsted Experimental Station, Harpenden, Herts (November 30).

SENIOR LABORATORY TECHNICIAN FOR SCIENCE DEPARTMENT, having chemistry, physics and biology laboratories and general and glassworking workshops—The Secretary, Paddington Technical College, Saltram Crescent, London, W.9 (November 30).

LECTURER IN PSYCHOLOGY at the University of New England, Australia—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Australia, December 13).

RESEARCH ASSISTANT (preferably with a postgraduate degree and suitable experience in biochemistry and microbiology) IN THE DEPARTMENT OF BACTERIOLOGY to assist in a programme of work on immunochemistry—The Registrar, The University, Manchester 13 (December 14).

SCIENTIFIC OFFICER (with a first- or second-class honours degree in chemistry or agricultural chemistry), for combined field experimentation and laboratory work on fertilizers and soil fertility problems (Ref. "A"); and an EXPERIMENTAL OFFICER (with a degree in chemistry or agricultural chemistry), to assist in research on crops and soils and in dealing with experimental data (Ref. "B")—The Secretary, Rothamsted Experimental Station, Harpenden, Herts, quoting appropriate Ref. (December 14).

LECTURER (with research experience in some branch of valve, transistor or circuit electronics, or in solid state physics, and preferably teaching experience) IN THE DEPARTMENT OF ELECTRONIC ENGINEER-

ING—The Secretary and Registrar, University College of North Wales, Bangor, North Wales (December 15).

LECTURER IN PHYSICS—Prof. C. C. Butler, Physics Department, Imperial College of Science and Technology, London, S.W.7 (December 16).

CHAIR OF MATHEMATICS tenable at Bedford College—The Academic Registrar, University of London, Senate House, London, W.C.1 (December 20).

RESEARCH OFFICER (with at least a university honours degree in science with physics or mathematics as a major subject, or in physical engineering or equivalent qualifications together with appropriate research experience) IN THE DIVISION OF ELECTROTECHNOLOGY, C.S.I.R.O., National Standards Laboratory, Sydney, Australia, to undertake research and to develop techniques and equipment for establishing standards of electrical measurements at high frequencies—Chief Scientific Liaison Officer, Australian Scientific Liaison Office, Africa House, Kingsway, London, W.C.2, quoting Appointment No. 760/88 (December 21).

ASSISTANT LECTURER (graduate of a British University or equivalent qualifications and experience) IN PHYSICS at the University of Hong Kong—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Hong Kong, December 31).

LECTURER IN EDUCATION at the University of Tasmania, Australia—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Australia, December 31).

DRUMMOND SENIOR FELLOW FOR RESEARCH IN NUTRITION—The Hon. Secretary, Drummond Trust, University College, Gower Street, London, W.C.1 (January 31).

ASSISTANT, Grade B (honours graduate in chemistry), TO TEACH CHEMISTRY at Bournemouth Municipal College of Technology and Commerce—Chief Education Officer, Town Hall, Bournemouth.

ASSISTANT, Grade B, TO TEACH CHEMISTRY WITH SOME PHYSICS OR MATHEMATICS—The Principal, North-West Kent College of Technology, Miskin Road, Dartford, Kent.

ASSISTANT, Grade B (with a good honours degree and preferably some previous teaching experience), FOR MATHEMATICS—The Clerk to the Governors, Mid-Essex Technical College and School of Art, Market Road, Chelmsford.

ASSISTANT, Grade B (with a good honours degree), FOR MATHEMATICS—The Clerk to the Governors, South-East Essex Technical College, Longbridge Road, Dagenham, Essex.

ASSISTANT HORTICULTURIST (with a horticultural degree or equivalent) IN THE POMOLOGY SECTION, for experiments in vegetable propagation—The Secretary, East Malling Research Station, East Malling, near Maidstone, Kent.

ASSISTANT RESEARCH OFFICER (with a university degree in mathematics or physics) IN THE NATIONAL TELECOMMUNICATIONS RESEARCH LABORATORY, South African Council for Scientific and Industrial Research, Johannesburg, for duties which include the compilation of ionospheric data and the preparation of radio propagation predictions—The South African Scientific Liaison Officer, Africa House, Kingsway, London, W.C.2.

ASSISTANT TECHNICAL SECRETARY (young graduate with scientific training) IN THE STEELMAKING DIVISION of the B.I.S.R.A., for research administration, liaison with industry, and the collection and presentation of information—The Personnel Officer, British Iron and Steel Research Association, 11 Park Lane, London, W.1, quoting "A.T.S.4".

BRIT FELLOW FOR SCIENTIFIC RESEARCH—The Registrar, Imperial College, South Kensington, London, S.W.7.

READER IN CHEMICAL ENGINEERING; a READER IN ENGINEERING PRODUCTION TECHNOLOGY—MATERIALS AND PROCESSES; and a READER IN AUTOMATIC CONTROL—APPLIED TO MACHINES AND PROCESSES—The Registrar, Loughborough College of Technology, Loughborough, Leicestershire, quoting "D.1".

SCIENTIFIC OFFICER (PETROLOGIST) (with a first- or good second-class honours geology degree and at least five years postgraduate experience in petrology) IN THE GEOLOGICAL SURVEY DEPARTMENT, Federation of Nigeria, for duties which include petrological and mineralogical work in the Geological Survey laboratories—The Director of Recruitment, Colonial Office, London, S.W.1, quoting BCD.105/14/04.

SCIENTIFIC OFFICERS (preferably under 45 years of age, with a good honours degree in natural science and preferably postgraduate experience in fishery research) IN THE FISHERY DEPARTMENT, Sierra Leone, to undertake research on fishery problems—The Director of Recruitment, Colonial Office, London, S.W.1, quoting BCD.65/15/01.

SENIOR SCIENTIFIC/SCIENTIFIC OFFICER (with a first- or second-class honours degree in physics or metallurgy or equivalent qualification, and preferably experience in the field of metallic coatings), to carry out research and development work on the electro-deposition of metals—The Senior Recruitment Officer, Atomic Weapons Research Establishment, Aldermaston, Berkshire, quoting Ref. B/1428/2/34.

STATISTICIAN (with a good honours degree in mathematics), for biometrical research and consultation in the Section of Statistics—The Secretary, National Institute for Research in Dairying, Shinfield, Reading, quoting Ref. 57/9.

TECHNICIAN IN THE DEPARTMENT OF BOTANY—The Registrar, University College of Wales, Aberystwyth.

REPORTS and other PUBLICATIONS

(not included in the monthly Books Supplement)

Great Britain and Ireland

Building Research Station Digest No. 101 (August, 1957): The B.S.2660 Range of Colours. Pp. 6. (London: H.M. Stationery Office, 1957.) 3d. [189

General Electric Co., Ltd. Atomic Power Achievements. Pp. 36. The Chairman's Address at the Fifty-seventh Annual General Meeting, London, September 5th, 1957. Pp. 16. (London: General Electric Co., Ltd., 1957.) [189

Government of Northern Ireland: Ministry of Agriculture. Leaflet No. 74: Flax Variety Trials. Pp. 6. Leaflet No. 109: The Cultivation of Black Currants. Pp. 6. (Belfast: Ministry of Agriculture, 1957.) [189

British Internal Combustion Engine Research Association. Fourteenth Annual Report, 1st April, 1956–31st March, 1957. Pp. 22. (Slough: British Internal Combustion Engine Research Association, 1957.) [189

Scientific Proceedings of the Royal Dublin Society. Vol. 27 (N.S.), No. 13 (22 May, 1957): A Tertiary Deposit in County Tipperary. By W. A. Watts. Pp. 309–312. 1s. No. 14 (15 July, 1957): Sand Volcanoes, Sheet Slumps and Stratigraphy of Part of the Slieveardagh Coalfield, County Tipperary. By W. E. Nevill. Pp. 313–324+plates 11–13. 4s. No. 15 (23 July, 1957): Award of the Boyle Medal to Professor Robert McKay, D.Sc. Pp. 325–330. 1s. Economic Proceedings of the Royal Dublin Society. Vol. 4. No. 3 (19 June, 1957): Propagation of Eelworm-Free Stocks of Strawberry Runners. By J. Carroll, Jean McKay and Mary Hannigan. Pp. 75–82+plate 15. 2s. (Dublin: Royal Dublin Society, 1957.) [189

Other Countries

Suomen Geodeettischen Laitoksen Julkaisuja: Veröffentlichungen des Finnischen Geodätischen Institutes. No. 48: Beobachtungsergebnisse der Finnischen Triangulationen in den Jahren 1947–1952. Pp. 95. (Helsinki: Finnischen Geodätischen Institutes, 1957.) [189

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Bulletin of the Florida State Museum, Biological Sciences. Vol. 2, No. 3: A Taxonomic Reappraisal of the Turtle *Pseudemys alabamensis* Baur. By Archie Carr and John W. Crenshaw, Jr. Pp. 25–42. 30 cents. Vol. 2, No. 4: *Acanthurus randalli*, a New Surgeon Fish from the Gulf of Mexico. By John C. Briggs and David K. Caldwell. Pp. 43–52. 25 cents. Vol. 2, No. 5: Two Pleistocene Mammalian Faunas from Alachua County, Florida. By Robert S. Bader. Pp. 53–76. 45 cents. (Gainesville, Fla.: Florida State Museum, 1957.) [189

Annalen van de Sterrewacht te Leiden. Deel 18, Vierde stuk: Meridian Observations of Double Stars. By G. Van Herk. Pp. i+30. Deel 21, Eerste stuk: SV Camelopardalis, an Eclipsing Binary with Variable Light-Curve. By H. Van Woerden. Pp. 114. Deel 21, Tweede stuk: Photographic Magnitudes of 15651 Stars Brighter than about 10·5 Magnitude in the Southern Selected Areas, derived from Plates taken by Dr. A. J. Wesselink. By C. J. Kooreman and P. Th. Oosterhoff. Pp. 115–214. (Leiden: Staatsdrukkerij- en Uitgeverijbedrijf, 1957.) [189

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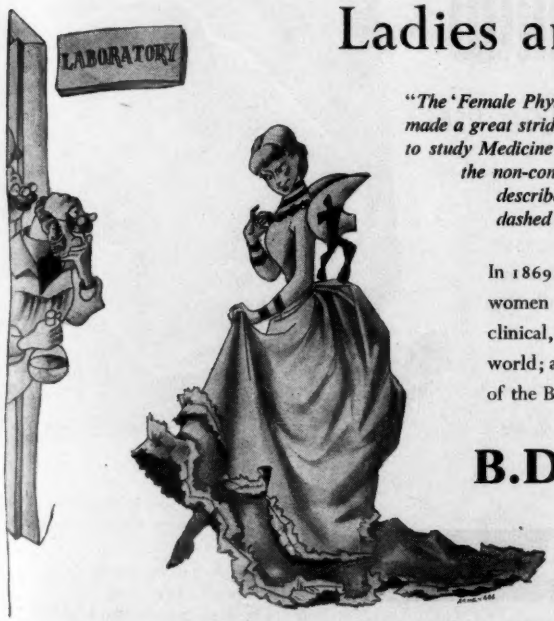

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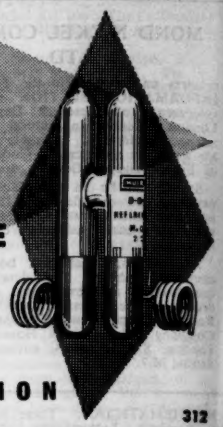

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